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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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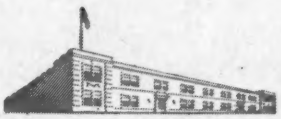

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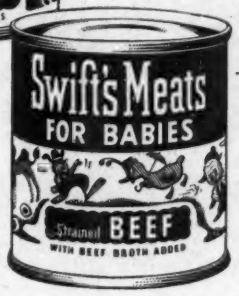

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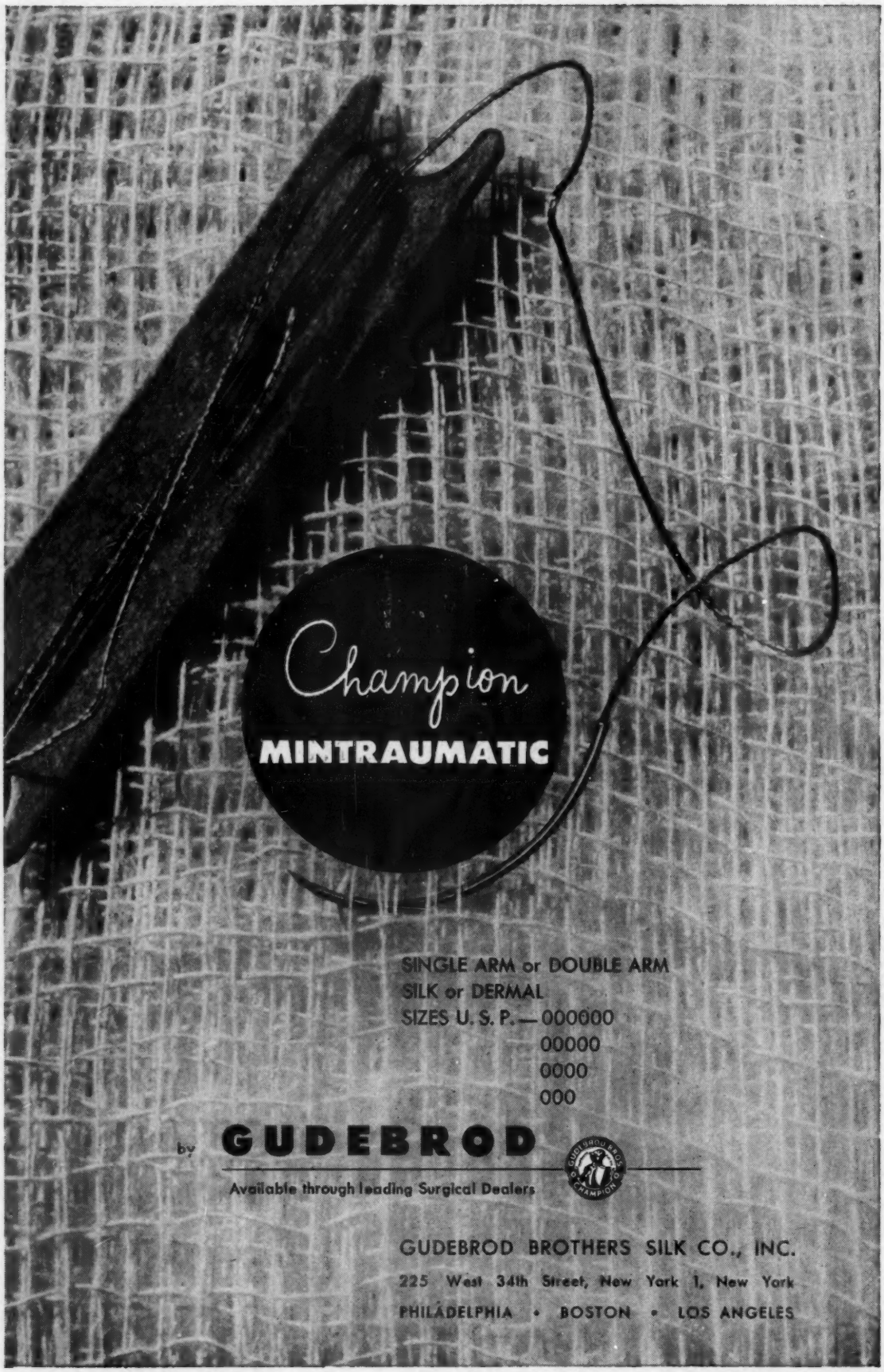
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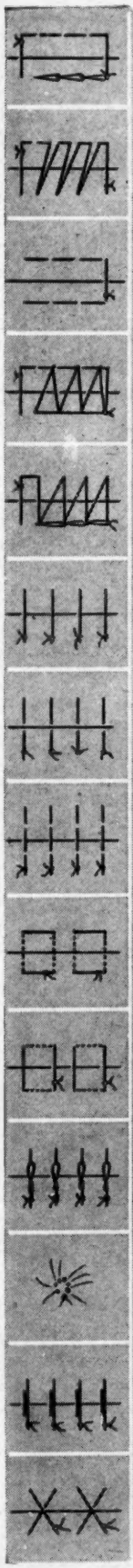

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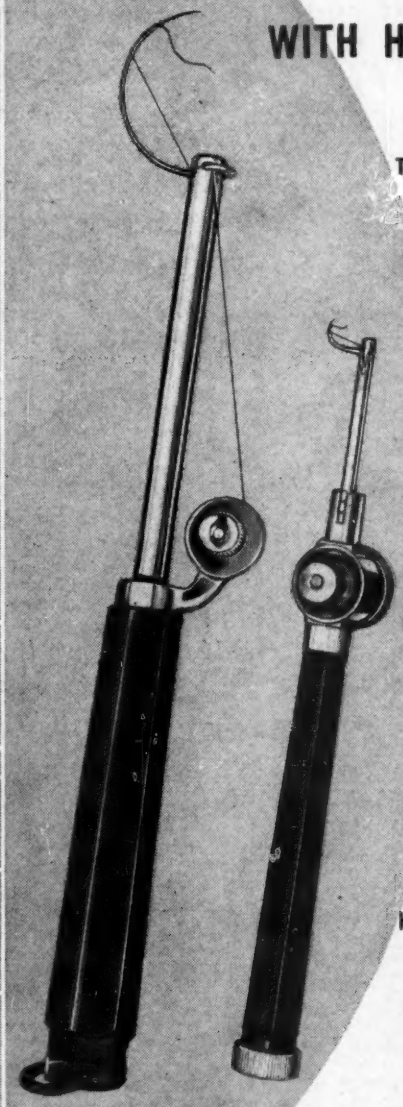

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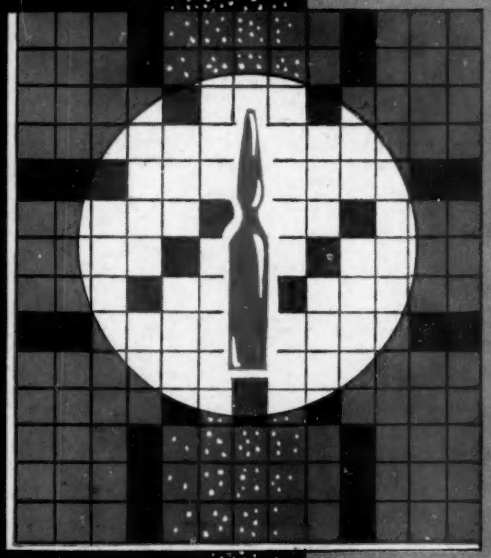

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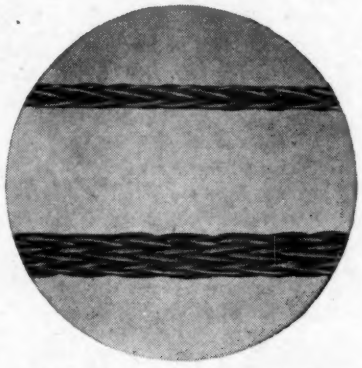

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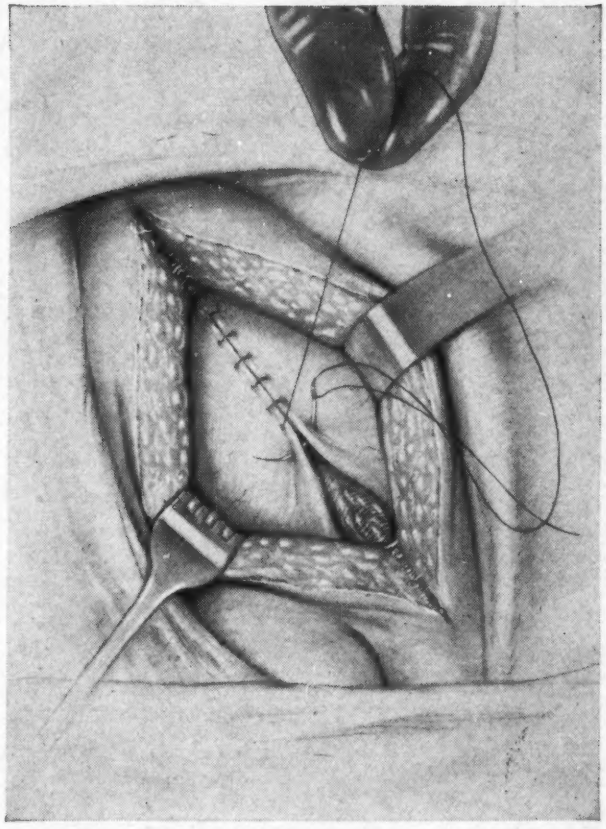

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Original Communications

ANATOMIC VARIATIONS OF THE VAGUS NERVES— THEIR SIGNIFICANCE IN VAGUS NEURECTOMY

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DURING recent years there has been an increasing interest in the role of the psychic factors in peptic ulcer. The degree of the psychic influence is not known, but that it is of importance is generally accepted today. On the assumption that the psychic factors as contributors to the cause and continuation of chronicity of peptic ulcers are mediated through the vagus nerves it has been thought logical also to assume that interruption of the vagus nerves would curtail the added gastric secretions and motility. In contradistinction to the earlier views of Beaumont and Pavlov, that in the absence of food or psychic stimuli the gastric glands are quiescent, the work of Carlson[1] indicates that there is a continuous secretion of gastric juice in the normal individual and that this occurs even in prolonged fasting. Thornton, Storer, and Dragstedt[2] have shown that there is an abnormality in the secretion of gastric juice in most if not all ulcer patients, the continuous secretion being abnormally high in the absence of stimulation by food or psychic factors and they further state that the most pronounced increase over the normal is noted in the volume and acidity of the continuous night secretion. There is also excessive motility of the stomach in many ulcer patients and both contribute to the cause and maintenance of chronicity of peptic ulcers. Both hypermotility and hypersecretion, the latter the more important of the two, are diminished following section of the vagus nerves.

Early descriptions of vagotomies for various therapeutic purposes were reported by Exner and Schwartzman[3] in 1912, Stierlin[4] in 1920, Latarjet[5] and Bircher, in 1921, and Schiassi[7] in 1925. Most, if not all, of these vagotomies were incomplete. Hartzell[8] in 1929 reported a decrease in acid secretion following intrathoracic complete vagotomies in dogs. Wilhelmj, McCarthy, and Hill[9] performed partial gastrectomy and complete vagotomy on four dogs in 1936

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and reported lower average acid curves than those on which partial gastrectomy alone was performed. Weinstein and associates[10] studied the behavior of three types of gastric pouches in dogs, the Heidenhain pouch with no vagus innervation, the Pavlov pouch with only a small percentage of the vagus fibers intact, and a "vagal" pouch in which practically all vagus fibers were unsevered. Their experiments showed essentially the same acidity curves for all types of pouches in response to the ingestion of food, but when a stimulus was used, which operated through the central nervous system, the innervated pouches responded with acidity curves which were high, while the noninnervated Heidenhain pouch did not respond at all. Weinstein and his co-workers pointed out the importance of complete vagotomy, recommended transthoracic approach rather than abdominal, and stressed the great technical difficulty of performing a complete vagotomy.

Since 1943 when Dragstedt and Owens[11] reported improvement in three cases of peptic ulcer following bilateral supradiaphragmatic vagotomies, there has been a steady increase in the numbers of patients on whom this operation has been performed with good immediate results. This fact is distinctly evident from the reports of Dragstedt and his co-workers at the University of Chicago and from the reports of Grimson, Moore, and others.[12-21] Although it is generally agreed that the procedure is not the final answer to the treatment of peptic ulcer, the results are decidedly encouraging and the operation is obviously useful in many selected cases, particularly young patients with no serious stenosis, hemorrhage, hypermotility, or hypersecretion and in those who have been resistant to medical treatment. Postoperative complications have been rarely reported although the gastric atony which follows vagotomy in some cases must yet be fully evaluated. In the vast majority of the cases there has been early decrease in the volume and acidity of the gastric secretions, a decrease in the gastric motility and a prompt and dramatic relief of ulcer pain following vagotomy.

The operation, as it is generally performed today, is essentially the same in most hands. By a transthoracic approach, through the bed of the left eighth or ninth rib, the pleura over the posterior mediastinum is incised, the supradiaphragmatic portion of the esophagus mobilized, and the anterior and posterior vagus nerves immediately above the level of the diaphragm are located, mobilized, and divided. A segment of the proximal portions of each of the nerves is removed and the remaining proximal ends are sutured to the posterior pleura, outside of their normal pathways, to exclude the possibility of early regeneration. The technique described by Grimson and associates[17] is to dissect the nerve trunks for a distance of about 10 or 12 cm. above the diaphragm and at this level ligate and divide them. Traction is then put on the distal segments and the nerves are tied and divided at the level of the diaphragm, the tied ends retracting below the diaphragm. It is thought that the defect in the vagus nerves lessens or prevents late functional nerve regeneration without transplanting the nerves as has been suggested by Dragstedt. Moore and his co-workers[20] opened the diaphragm and resected a portion of each nerve from

just below the lung root to the mid-portion of the gastric fundus. Transthoracic vagotomy is at present being used more widely than the transabdominal approach, although Dragstedt and his co-workers have had wide experience with both approaches. There is still some question as to whether or not the abdominal approach offers the same opportunity of accomplishing complete bilateral vagus neurectomy which is offered by the transthoracic route.

The literature adequately presents the experimental and clinical data which have led to the present acceptance of this procedure as an important new treatment of peptic ulcer by many of the nation's leading surgeons. The technique of the operation, reports of the immediate results following the procedure, and interpretations of the possible physiologic mechanics involved are to be found in the literature, but it is worthy of note that there is a decided scarcity of material on anatomic descriptions of the vagus nerves and their branches between the levels of the main-stem bronchi and the diaphragm. Few have pointed out the rather striking variations of the vagus nerves in the immediate supradiaphragmatic levels. That these variations do occur is a definite fact and that they may be of sufficient magnitude to cause failure in accomplishing complete vagotomies in some cases must be recognized. Dragstedt has pointed out the importance of sectioning the vagi immediately above the diaphragm when transthoracic approach is used and has mentioned the necessity of dividing all of the fibers coursing to the stomach. He has further pointed out the fact that anatomic variations are to be found in some cases. After our work was well under way we learned that Edwin M. Miller,* in discussing a paper presented by Storer and associates[19] at a meeting of the Central Surgical Association in February, 1946, stated that great variations in the distribution of the branches of the vagus nerves at the supradiaphragmatic levels were found in dissections of a number of cadavers and he presented lantern slides illustrating some of the anatomic variations which he had observed. Some weeks prior to the completion of our work we received word of the presentation of a paper entitled "Anatomic Distribution of the Vagus Nerves at the Lower End of the Esophagus in Relation to Gastric Neurectomy for Ulcers." It was presented by Waltman Walters at a meeting of the Western Surgical Association in December, 1946, and represented the work of Walters, Bradley, Small, and Wilson.* The work has not as yet been published and we do not know the details of their observations, but from word received, they found distinct variations in the distribution of the vagus nerves at the supradiaphragmatic levels and in some cases they were sufficiently variable to be of considerable clinical significance.

Anatomic descriptions of the course of the vagus nerves are to be found in standard anatomy texts but these descriptions lack minute and accurate de-

*Since the completion of this paper two articles have appeared in the J.A.M.A. 133: 459, 461, 1947. One, entitled "An Anatomic Study of the Vagus Nerves" by Edwin M. Miller and Carl B. Davis, represents the work reported by Miller at a meeting of the Central Surgical Association in February, 1946. The other, entitled "Anatomic Considerations of Gastric Neurectomy" by William F. Bradley, John T. Small, James W. Wilson, and Waltman Walters, apparently represents the work reported by Walters at a meeting of the Western Surgical Association in December, 1946. The latter authors have made somewhat different interpretations of their dissected material than we have made from our material.

tails of the nerves at the levels just mentioned. Baptista[22] presented an excellent and detailed description of dissections of the vagi in vertebrates, in which cats were the mammalian representatives. The course of the vagus nerves from the hilar level to the stomach which we herewith present is based on text material,[23-25] Baptista's findings, and our own observations (Fig. 6). The vagi pass caudad as single trunks along either side of the trachea then dorsal to the mainstem bronchi at which level they give off pleuropulmonary, tracheobronchial, and vascular fibers. The respective nerve trunks then course medially to either anterolateral aspect of the esophagus, and at the level immediately below the bronchi each nerve divides into anterior and posterior branches, the anterior branches of each nerve joining to form the anterior esophageal plexus and the posterior branches joining to form the posterior esophageal plexus. As a general rule it may be said that the major part of the anterior esophageal plexus consists of fibers from the left nerve, and the major part of the posterior plexus consists of fibers from the right nerve. Numerous fibers are given off from both anterior and posterior plexuses which enter the esophagus and we observed many fibers derived from the anterior plexus which entered the pericardium at various levels. In addition to the pericardial and esophageal branches the plexuses also give off pleuropulmonary and vascular fibers. In the descriptions of the course and general character of the nerves at these levels which we have found, the gastric divisions of the vagi are reported as single trunks, one, the left, or anterior nerve, and the other, the right, or posterior nerve. The anterior nerve is described as coursing along the antero-left lateral aspect and the posterior nerve along the postero-right lateral aspect of the lower esophagus to the diaphragm, at which level they pass through the hiatus and are distributed to the stomach, the anterior supplying the anterior aspect and the posterior nerve supplying the posterior aspect of the stomach. In contradistinction to this we found rather marked variations in the anatomic appearance of the gastric divisions of the vagi in many cases, details of which will appear elsewhere in this presentation. We found that there are, in all cases, an anterior, or left nerve trunk or nerve complex, and a posterior, or right nerve trunk or nerve complex, formed respectively from the anterior and posterior esophageal plexuses. The anterior courses along the esophagus on its antero-left lateral aspect, the nerve or nerves varying in location in most cases from the anterior midline to a point just medial to the true left lateral position, and the posterior courses along the right postero-lateral aspect of the esophagus, varying in location, in most cases, from the posterior midline to a point just medial and posterior to the true right lateral position. The anterior and posterior nerves or complexes then pass through the hiatus and divide into branches, some of which supply, respectively, the proximal portions of the anterior and posterior aspects of the stomach and some of which course to the proximal part of the lesser curvature where they anastomose and continue distally along the lesser curvature, many of the fibers coursing within the fat and fascia of the gastrohepatic ligament. From here, fibers are given off at regular intervals, which course downward, more or less at right angles to the lesser curvature and supply the anterior and

posterior portions of the stomach. The distribution of the vagus fibers to the stomach as described here is of importance in that it explains, for the most part, the early failures in accomplishing complete vagus sections. It was previously thought that the anterior and posterior gastric nerves were distributed over the gastric walls, and the fact that the nerves course through the gastrohepatic ligament at the lesser curvature and along this course give off branches to the anterior and posterior gastric surfaces was not taken into account. Because of this fact the early transabdominal vagotomies were incomplete inasmuch as complete vagal continuity was not interrupted, the fibers coursing through the gastrohepatic ligament having been left intact. This point has recently been mentioned by Dragstedt[26] and our dissections substantiate his observations.

For the study and analysis herewith presented, fifty esophagi* were removed at necropsy, the specimens including the lower trachea, main-stem bronchi, and a portion or all of the stomach in as many cases as was possible. A few specimens obtained early in the course of the work were studied and dissected in the fresh state but it was later considered advisable to complete the studies on fixed specimens inasmuch as more accurate evaluation of all fibers could thereby be made. The ages of patients from which specimens were removed ranged from 2 to 80 years and the ratio of males to females was approximately equal. Body sizes were, of course, variably represented and there was no apparent relationship between body sizes and the sizes and character of the nerves. The course of the vagi from the level of the primary bronchi to the stomach was studied, general structure of the so-called esophageal plexuses was noted, and the general relationship of the nerves to the stomach was examined in a number of specimens, but special emphasis was placed on the study of variations in appearance, formation, and distribution of the gastric divisions of the vagi which form from the anterior and posterior esophageal plexuses and course to the stomach through the esophageal hiatus.

For purposes of simplification a classification was decided upon which would enable us to place the specimens studied into classes based on certain major anatomic variations of the gastric divisions of the vagus nerves at the supradiaphragmatic levels. The classification is as follows:

I. *Simple* or *basic pattern,* in which a single, primary trunk forms from the anterior and posterior esophageal plexuses forming thereby the so-called left, or anterior, and the right, or posterior, nerves and entering the hiatus as single trunks. The classification of the specimens is based on the general character of the nerve or nerve complex between the levels of the esophageal plexus and the upper level of the diaphragm (Figs. 1, 2, and 3).

II. *Intermediate pattern,* in which a single, primary trunk forms from the anterior and/or the posterior esophageal plexus or plexuses but divides into two or more secondary nerve trunks before entering the hiatus in their course to the stomach (Figs. 4 and 5).

*We should like to express our appreciation of the cooperation of the Medical Examiner's Office, New York, N. Y., for having furnished us with the majority of the specimens studied.

Fig. 1.—Dissected specimen illustrating anterior (left) and posterior (right) views of the esophagus with attached primary bronchi, pericardium, and a portion of the diaphragm. The branches of the vagus nerves appear in black. This specimen presents anterior and posterior examples of the simple pattern, in which a single nerve trunk forms from the esophageal plexus and enters the esophageal hiatus.

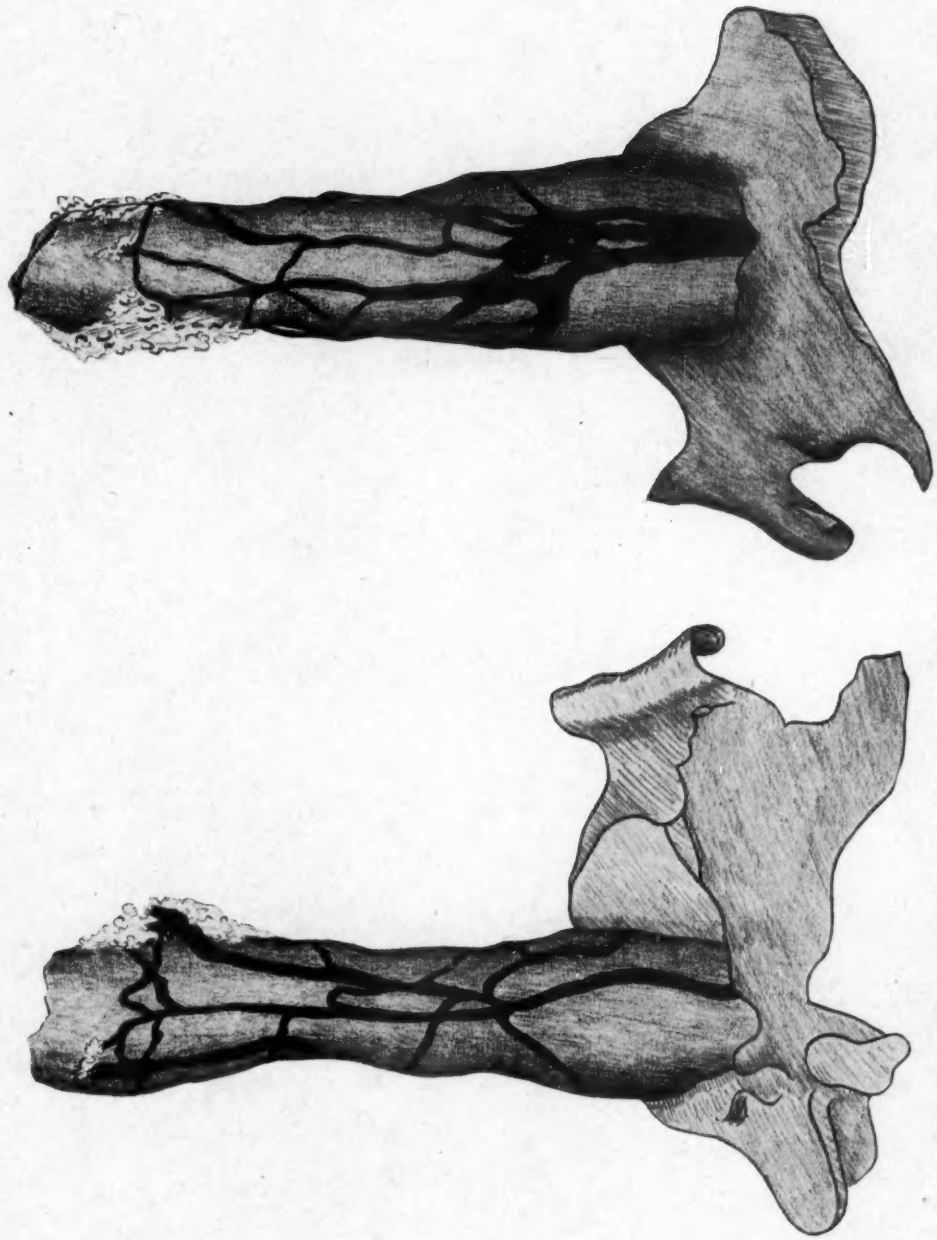

Fig. 2.—Anterior view (left) and posterior view (right) of the esophagus and portion of the diaphragm illustrating another variety of the simple pattern. Note the marked difference in the size and general appearance of the anterior, or left, and the posterior, or right, gastric nerves.

Fig. 3.—Right lateral view (left) and anterior view (right) of a specimen presenting the simple pattern of both nerves and illustrating the very unusual and enormous sizes of the gastric nerves and of the fibers of the esophageal plexuses occasionally seen.

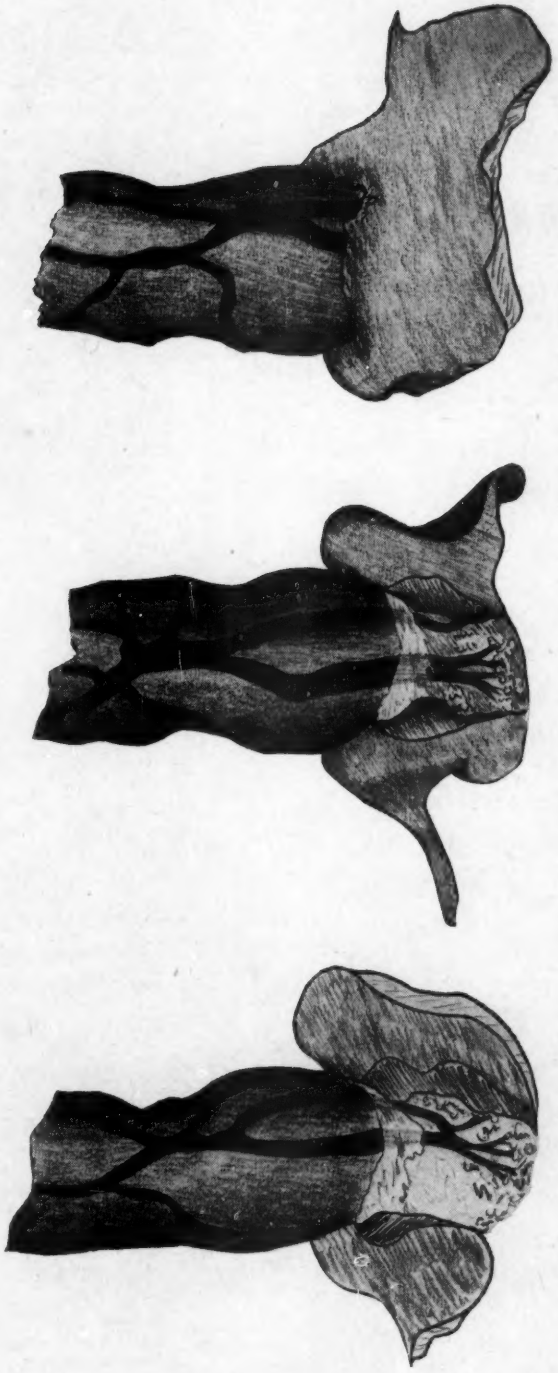

Fig. 4.—Three specimens: an anterior view (left) and posterior views (center and right), illustrating slight variations of the intermediate pattern, in which a single trunk forms from the esophageal plexus and divides into secondary divisions before entering hiatus. Note, in two of the specimens, the distribution of the nerves within the hiatus and below the diaphragms.

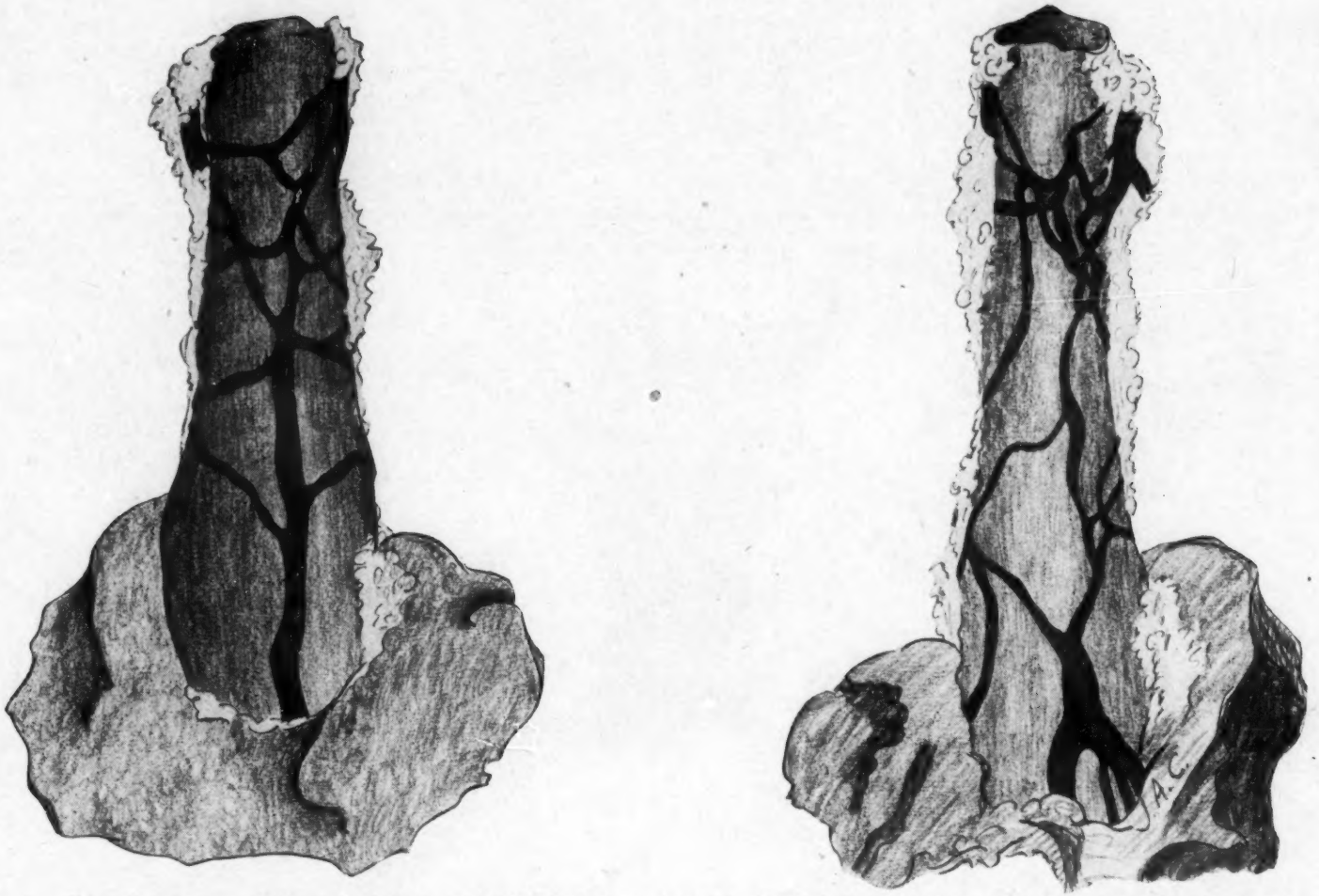

Fig. 5.—Anterior (left) and posterior (right) aspects of a specimen illustrating an anterior, or left, nerve of the simple pattern and a posterior, or right, nerve complex of the intermediate pattern. In the intermediate pattern, note the primary trunk and the four secondary divisions entering the esophageal hiatus.

III. *Complex pattern,* in which two or more primary trunks form from the anterior and/or the posterior esophageal plexus or plexuses before entering the esophageal hiatus in their course to the stomach, regardless of the number or character of the secondary nerve trunks (Figs. 6 to 10).

In placing the specimen in any part of the classification, inasmuch as the anterior and posterior nerve complexes may differ in class, the classification is made on the basis of the more complicated of the two nerve complexes.

Table I shows the classifications into which the various specimens were placed, the number and percentage of specimens which had anterior and posterior nerve trunks or nerve complexes of the same type, the number and percentage of nerves at the immediately supradiaphragmatic levels which were in "normal" positions, those which were found in "abnormal" positions, and those

TABLE I

	NUMBER	PER CENT
Classification of specimens:		
Pattern I (Simple)	30	60
Pattern II (Intermediate)	8	16
Pattern III (Complex)	12	24
Specimens having anterior and posterior nerves or nerve complexes of the same pattern:		
Pattern I	30	60
Pattern II	0	0
Pattern III	2	4
Positions of the gastric nerves or nerve complexes:		
Anterior (left) nerve or complex:		
Normal position*	44	88
Abnormal position*	6	12
Complexes, one fiber of which is out of the normal position	0	0
Posterior (right) nerve or complex:		
Normal position	41	82
Abnormal position	9	18
Complexes, one fiber of which is out of the normal position	3	
Gross morphology of nerve trunks immediately above diaphragm:		
Oval	92	73
Flat	34	27
Round	0	0
Widths of nerve fibers at upper level of diaphragm:		
0.1 to 0.15 cm.	13	10.3
0.2 to 0.25 cm.	33	26.1
0.3 to 0.35 cm.	33	26.1
0.4 to 0.45 cm.	20	16.0
0.5 to 0.6 cm.	22	17.5
0.8 to 0.9 cm.	5	4.0
Degree of prominence of nerve fibers below the esophageal plexuses:		
Prominent	88	70
Moderately prominent	21	16
Obscure	17	14
Levels of the lower limits of the anterior and posterior esophageal plexuses, measured from the upper level of the diaphragm:		
Under 1.0 cm.	5	5
1.0 to 2.0 cm.	33	33
2.0 to 3.0 cm.	36	36
3.0 to 4.0 cm.	17	17
4.0 to 5.0 cm.	5	5
5.0 to 6.0 cm.	3	3
6.0 to 6.5 cm.	1	1

*For explanation of terms normal and abnormal positions, see text.

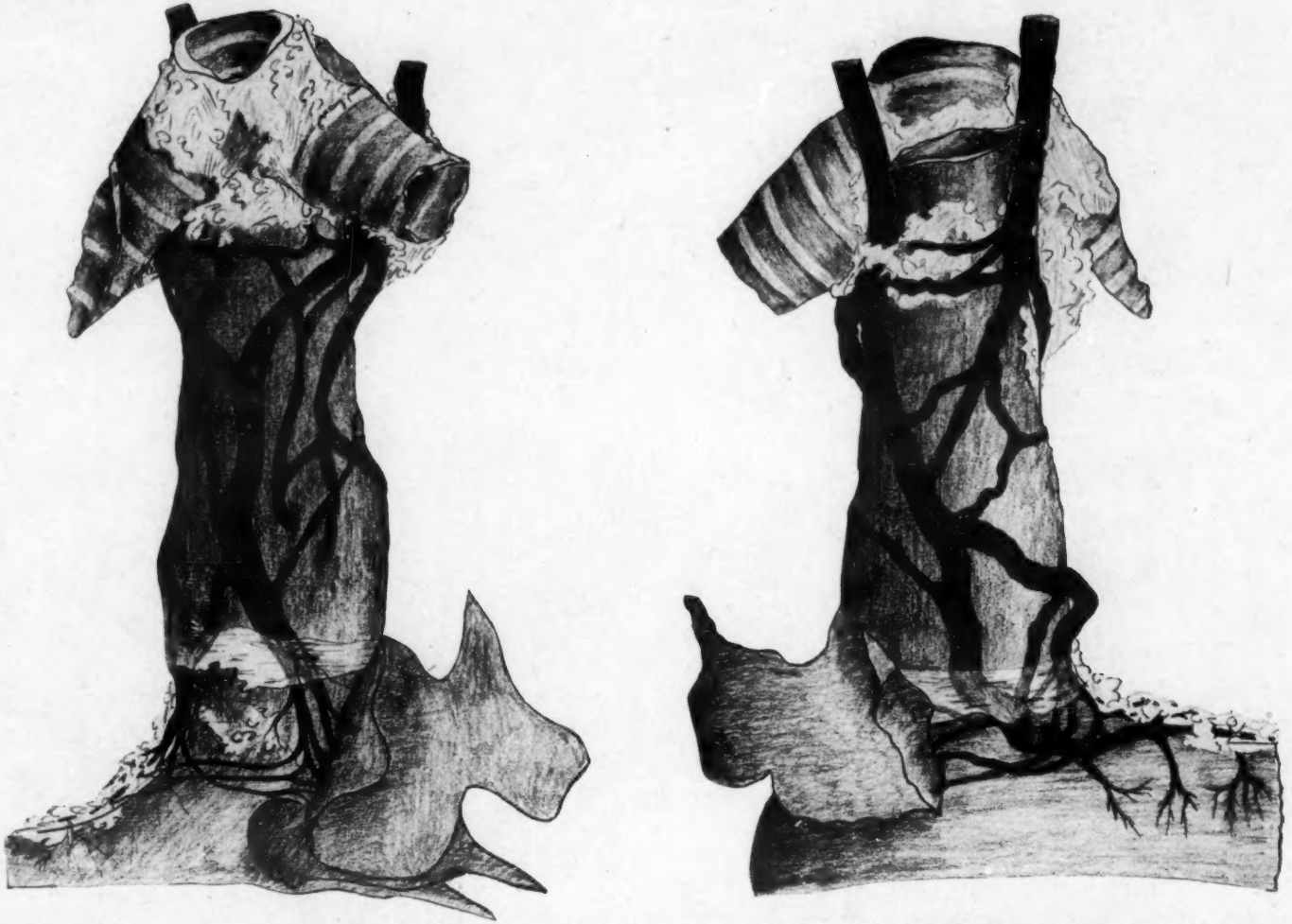

Fig. 6.—Anterior view (left) and posterior view (right) of a specimen which includes primary bronchi, esophagus, a portion of diaphragm, and the proximal part of the stomach. The complex pattern of gastric nerves is illustrated. Note the two primary trunks forming from the plexus on posterior aspect. Also note nerve distribution to and along lesser gastric curvature.

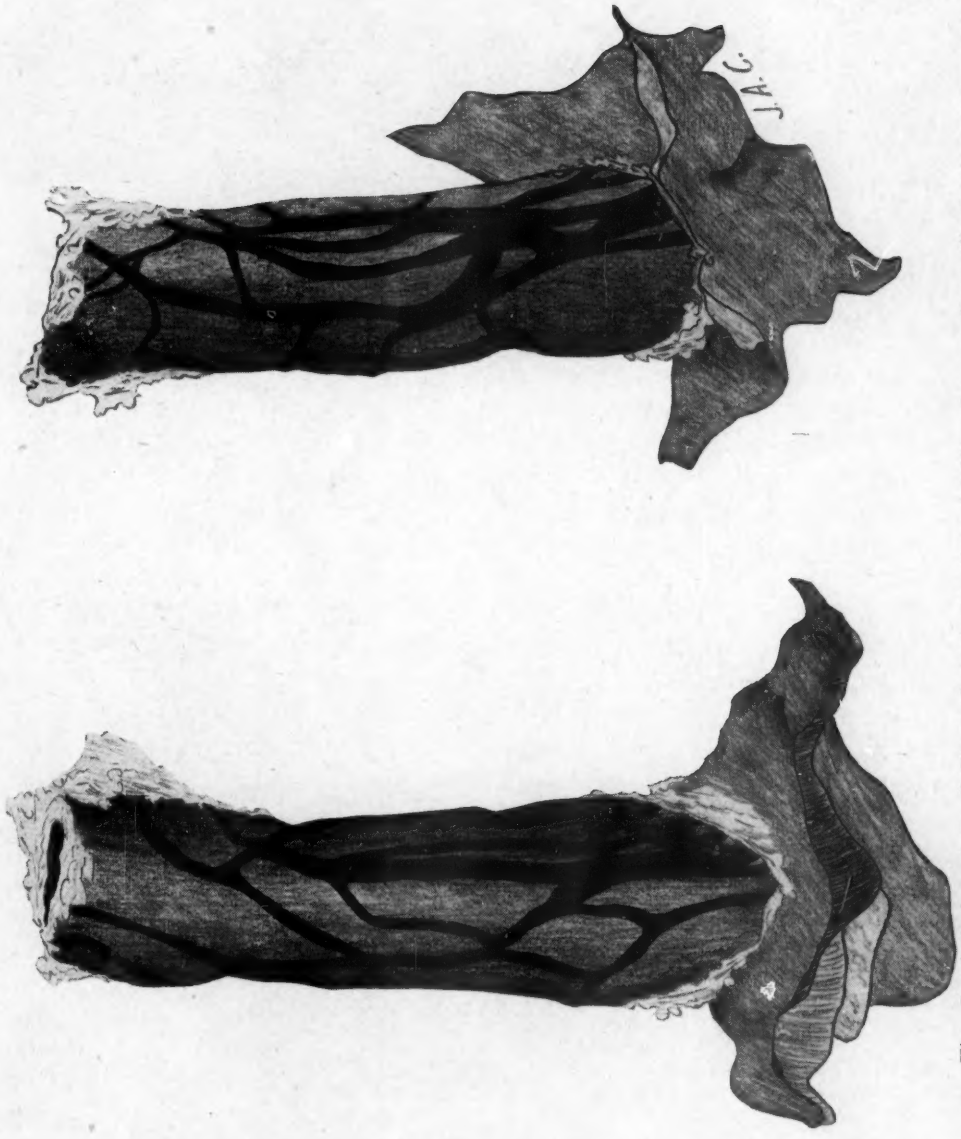

Fig. 7.—Anterior view (left) and posterior view (right) of a specimen illustrating very complex patterns of both anterior (left) and posterior (right) nerves. An example of patterns which might easily cause difficulty at operation.

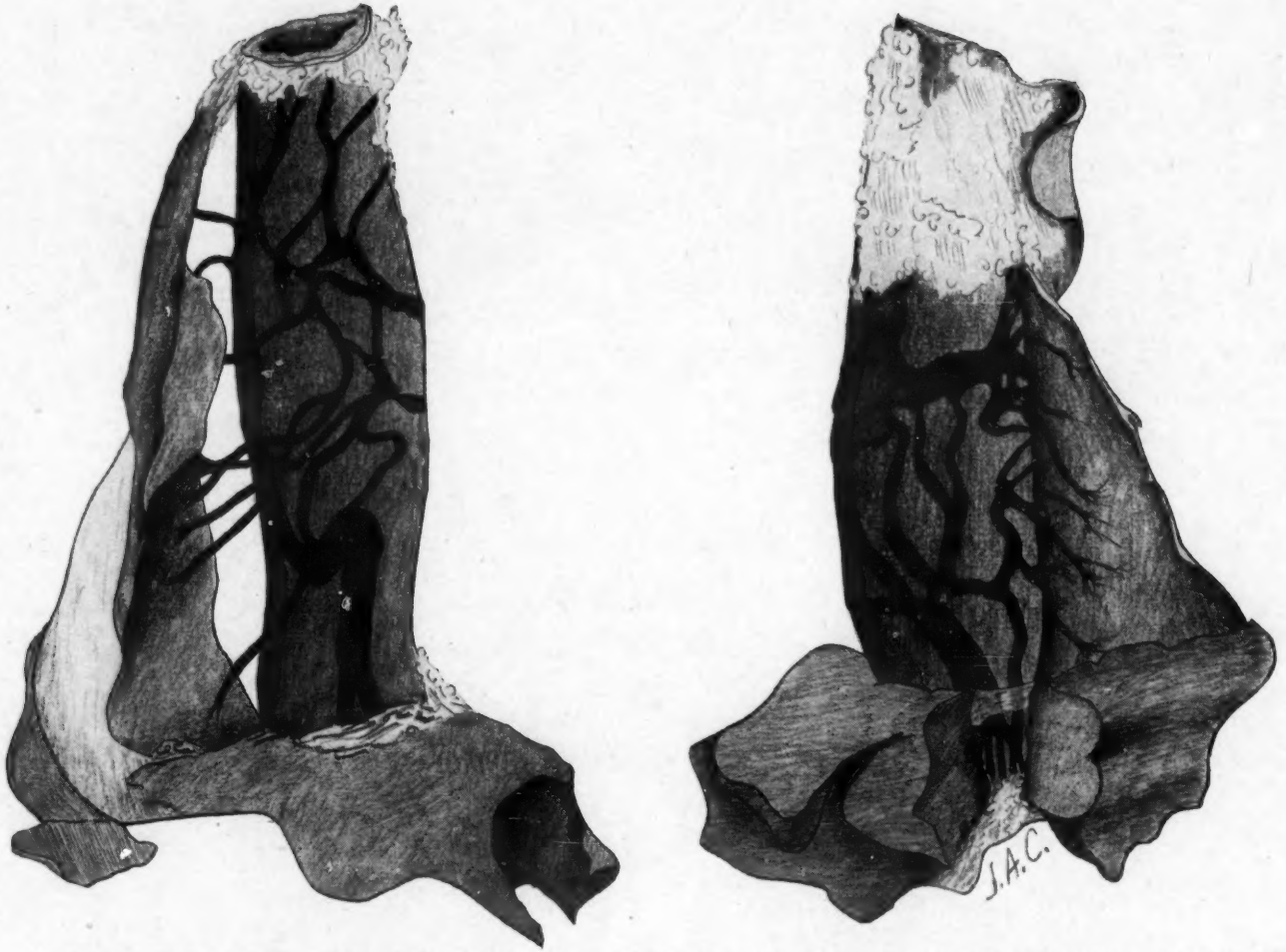

Fig. 8.—Anterior view (left) and posterior view (right) of a specimen with attached pericardium and portion of diaphragm which illustrates another variety of the complex pattern. Note the two primary trunks of the posterior nerve complex and the distribution of the latter within the hiatus.

which presented fibers of the nerve complexes which were in "abnormal" positions. The table also indicates the number and percentage of nerve fibers which presented certain morphologic characteristics, the numbers and percentages of nerve fibers which were in various ranges in regard to their width at the upper level of the diaphragm, the numbers of the fibers which were prominent, moderately prominent, or obscure in appearance and to palpation. Finally, it presents figures indicating at what levels above the diaphragm the anterior and posterior esophageal plexuses terminate and form the gastric divisions of the vagus nerves.

From the analysis of the material, it can be concluded that a distinct majority of the gastric divisions of the vagi are of a simple pattern, with a single trunk representing the left, or anterior nerve and a single trunk representing the right, or posterior, nerve. In our series, thirty specimens, or 60 per cent, were placed in this classification. Relatively few specimens fell into the intermediate classification. Eight specimens, or 16 per cent, were of this pattern, in which single trunks were formed from the anterior and/or the posterior esophageal plexuses but presented two or more secondary trunks which formed from the primary trunk before entering the esophageal hiatus. Twelve, or 24 per cent, of the specimens were of the complex pattern, in which there was more than one primary trunk formed from the anterior and/or the posterior esophageal plexuses. These figures suggest that a distinct majority of the cases encountered should present single gastric nerves which lack an immediately supradiaphragmatic complex and consequently present no technical difficulty in accomplishing a complete bilateral vagus neurectomy. The few intermediate types which one encounters should involve somewhat greater technical difficulty, in that the operator should attempt to locate the primary trunk of the complex and division should be made at this point. If this is not done and division is attempted above or below this level, one becomes involved in the fibers which make up a part of the complex esophageal plexus or in the multiple secondary trunks which enter the hiatus. One is thus confronted with the potential danger of incomplete division of all of the fibers coursing to the stomach. Inasmuch as this pattern does not occur in great numbers and since, with care in choosing the proper level for division, complete neurectomy should be accomplished, one need have little fear of operative failure. However, recognition of the fact that this pattern does occasionally occur is important. The fact that twelve, or 24 per cent, of the specimens were of the complex pattern should be taken seriously; a knowledge of these anatomic variations is essential and the clinical importance of the occurrence of these multiple primary trunk patterns should be recognized.

From Table I it may be noted that except for the specimens which were placed in the simple or basic group, the anterior and posterior nerves which are naturally of the same type, most cases encountered would present anterior and posterior nerve complexes which differ in pattern. Only two specimens of the intermediate and complex groups presented complexes of the same type.

As has been previously indicated, the most common location of the gastric nerves or nerve complexes has been found to be within an area just above the

diaphragm between the anterior midline and a point just anterior and medial to the true left lateral position for the left nerve, and between the posterior midline and a point just posterior and medial to the true right lateral position for the right nerve. These positions we have designated as normal and fibers of the gastric divisions of the vagi which have been found located outside of these areas we have designated abnormal in position. Of the anterior nerves or nerve complexes examined, forty-four, or 88 per cent, were found in the so-called normal position, and only six, or 12 per cent, of the specimens were in abnormal positions. Of the posterior nerves or nerve complexes, forty-one, or 82 per cent, were in normal position, and nine or 18 per cent, were in abnormal positions. Of the posterior nerves, three specimens presented com-

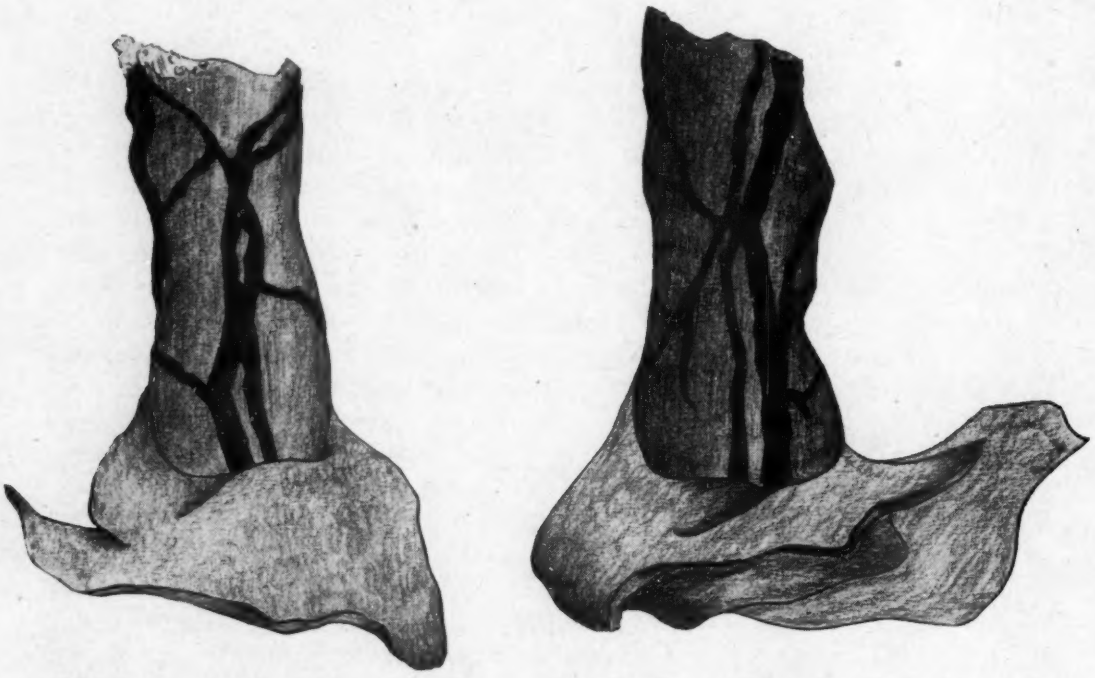

Fig. 9.—Anterior (left) and posterior (right) aspects of a specimen illustrating another variety of the complex pattern. Two primary trunks form from the posterior esophageal plexus.

plexes which were in normal position but each with a single fiber which was in an abnormal position. It is gratifying to note that the anterior and posterior gastric nerves usually are found within fairly limited areas. However, since there are occasional variations in their locations and since there are rather marked differences in the sizes of the nerves, some of which are quite obscure, one must recognize the fact that some fibers may be overlooked at the time of vagotomy and an incomplete division result.

As far as the gross morphology of the nerve fibers is concerned, ninety-two, or 73 per cent, were oval in shape and thirty-four, or 27 per cent, were flat, or ribbonlike. None of the nerves appeared as round fibers. Many of the flat fibers would be difficult to palpate and a few of these would be difficult to see

at operation, as is indicated later in the discussion of the number and percentage of obscure fibers noted in the series.

From the figures indicating the widths of fibers at the upper level of the diaphragm it may be seen that 52.3 per cent of the fibers were from 0.2 to 0.35 cm., and 33.5 per cent were relatively large, ranging from 0.4 to 0.6 cm. in width. Only 10.3 per cent were under 0.15 cm. and 3.9 per cent were over 0.8 cm. in width.

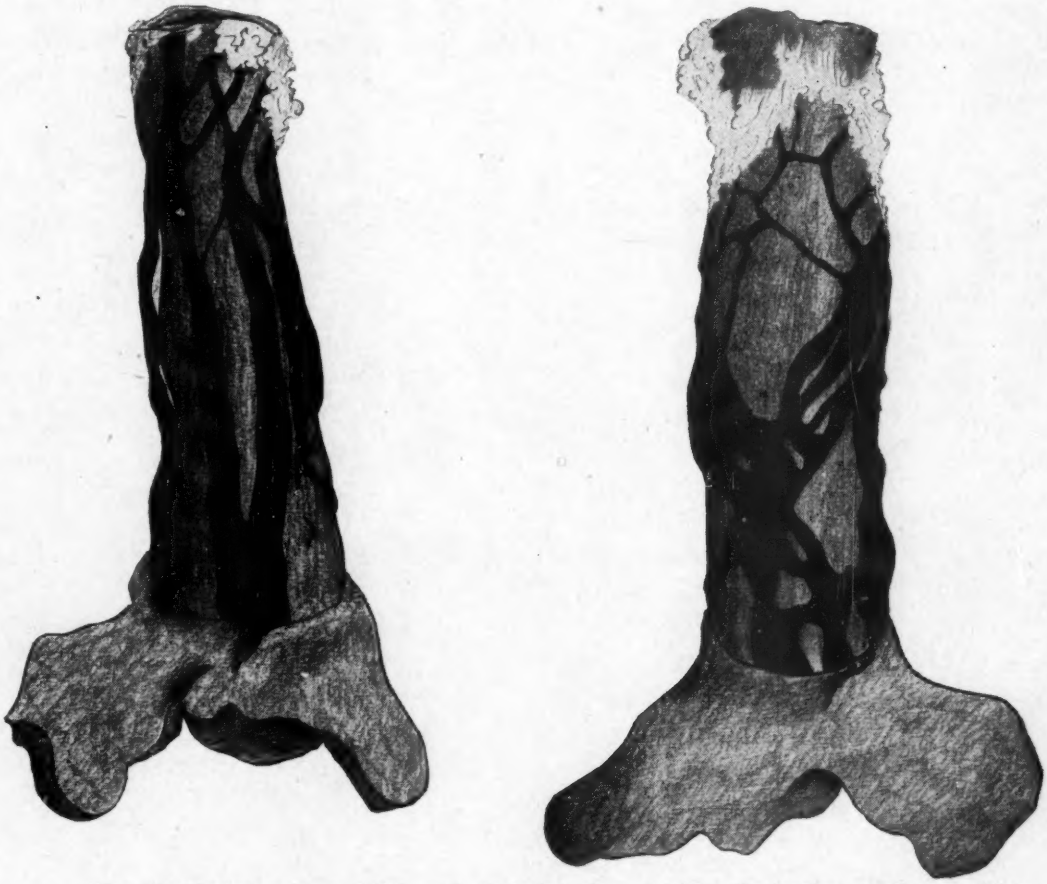

Fig. 10.—Anterior view (left) and posterior view (right) illustrating another variety of the complex pattern. Note the unusually complex posterior nerve pattern and the remarkably large nerve fibers.

Of the fibers examined, eighty-eight, or 70 per cent, were considered distinctly prominent and should have been easily palpated and visualized at operation; twenty-one, or 16 per cent, were moderately prominent but should have been easily demonstrable. Seventeen, or 14 per cent, were considered obscure and would have had to be sought for meticulously at the time of vagotomy.

The level of the lower limits of the anterior and posterior esophageal plexuses varied from 0.2 to 6.5 cm. above the upper level of the diaphragm; 69 per cent were from 1.0 to 3.0 cm., 17 per cent from 3.0 to 4.0 cm., and only 9 per cent were at higher levels, from 4.0 to 6.5 cm. It is important to have some idea

of the range of the lower limits of the plexuses inasmuch as the division of the nerves should be made below these levels in order to be more certain of locating and dividing all gastric branches of the vagi.

The more complicated patterns occur in sufficiently great numbers to justify serious consideration of the best methods of performing the vagus neurectomy in order to be more certain of complete division of all fibers. When the operator is certain that complete division is possible, if the primary gastric nerve trunks are divided, one would feel that this is the procedure of choice. However, if there is doubt, particularly when the pattern is very complex, it would seem that the procedure of choice would be, in effect, a "stripping" of the vagus fibers from the level of the hilum to the gastric fundus. Further, in view of the varied patterns and distribution of the gastric divisions of the vagus nerves, one would be led seriously to question the use of the abdominal approach as a routine procedure for vagotomy. For the surgeon who is only occasionally performing vagotomy this would seem particularly to apply.

SUMMARY

1. A brief review of the literature covering earlier work which has led to the use of the bilateral supradiaphragmatic vagus neurectomy in the treatment of selected cases of peptic ulcer is presented.

2. The present status and technique of bilateral vagus neurectomy in the treatment of peptic ulcer are briefly discussed.

3. The scarcity of published material on the anatomic details of the vagus nerves at the levels from the hilum to the upper limits of the diaphragm is pointed out.

4. The course and general anatomic features of the vagus nerves, from the primary bronchi to the diaphragm, are presented.

5. The details of the anatomic features of the vagus fibers which course from the anterior and posterior esophageal plexuses to the stomach are presented, the variations illustrated, and the clinical significance of these variations emphasized.

6. The routine use of the abdominal approach, particularly for the occasional performer of vagotomies, is questioned.

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SURGERY IN RADIATION INJURY OF THE STOMACH

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INTRODUCTION

IN A previous report[1] on radiation effects on the human stomach, it was pointed pointed out that very little is known relative to the effects of radiation on the human stomach. In the few human cases that have been reported[2, 3] in the literature concerning radiation injury to the stomach, the radiation injury occurred in stomach infiltrated with tumor where destruction of the tumor tissue was primarily responsible. In these cases, ulcer and perforation were reported following radiation. However, little can be learned about the clinical course and the laboratory studies in these patients who had radiation lesions of the stomach. The complicating factor of the pathologic lesions existing in the stomach prior to receiving radiation does not lend itself easily to an analogy with the experimental animal studies.

Various animals have been used to demonstrate the effect of radiation on the stomach. Engelstad[4] found distinct changes in the stomachs of rabbits after roentgen irradiation. A dose of 1,500 r. or more regularly produced ulcerations in the stomach coming on in the second to fourth week after radiation. Perforation was noted to have occurred frequently and in a few cases considerable hemorrhage from the ulcers was noted. If the animals lived more than two to three months after radiation, the ulcer showed a tendency toward healing and epithelization. Hueper and DeCarvajal-Forero[5] administered radiation in doses of 300 r. up to a total of 6,000 r. to the stomach of dogs and within four weeks produced marked loss in body weight, a moderate to severe anemia, and perforating gastric ulcers. Another series of dogs that received a total of 4,875 r. given over a twenty-five week period did not reveal any abnormal significant gross and histologic changes of the internal organs.

We have been able to observe cases of massive irradiation to the epigastric area in patients in whom there was no gastric pathology or history of previous gastrointestinal disease. All these patients were receiving radiation for metastatic retroperitoneal lymph nodes from testicular tumors or for prophylactic treatment of the retroperitoneal lymph nodes which are the first in the chain of metastasis from testicular tumor. All these patients had no previous history or symptomatology that could be remotely connected with the stomach and the results obtained in the treatment of their primary diseases have afforded, coincidentally, a human analogy to and confirmation of the experimental animal work on the irradiation of stomachs.

MATERIAL

As pointed out in a previous paper,[1] complications that required surgery were noted in two cases. Since that time, four other patients have had gastric surgery and in this paper we are presenting this series of cases. In Table I is

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listed an outline of the data in this series. Specimens obtained at operation in these necessary surgical procedures have added a great deal of information to the pathologic studies of these stomachs. Surgery in cases of a similar nature has not been previously reported elsewhere.

TABLE I

PATIENT	DOSAGE IN R. AT LEVEL OF D_{11} AND DAYS TO COMPLETE	PARTIAL GASTRECTOMY DONE DAYS AFTER COMPLETION OF RADIATION	OPERATIVE FINDINGS
1. C.	6,456 r. in 32 days	95	Perforation of a 3 cm. ulcer on posterior wall of antrum (Fig. 1)
2. Tr.	5,880 r. in 44 days	169	Thickened mucosa, submucosal ecchymosis, and generalized petechial hemorrhages of gastric mucosa (Fig. 2)
3. H.	5,304 r. in 55 days	155	Ulcer 2 cm. in diameter and 2 mm. deep proximal to the pyloric ring found. Mucosa contained petechial hemorrhages (Fig. 3)
4. Y.	6,105 r. in 49 days	190	Perforated ulcer 2 cm. in diameter found on the posterior antral wall (Fig. 4)
5. B.	5,096 r. in 54 days	189	On the posterior wall and involving the pyloric ring, a sharply demarcated ulcer 1½ cm. in diameter was found (Fig. 5)
6. Ty.	4,800 r. in 53 days	223	Peritonitis resulting from subacute perforation with abscess formation of a 3 by 3 by 2 cm. irregularly triangular ulcer in the antrum

In the first three cases reported, surgery was done as a life-saving measure in the treatment of gastric hemorrhage which occurred as a complication of radiation injury. The first case led us to the awareness that such a complication could occur since no previous similar case has been reported in the literature. With this awareness in mind, careful observation of other patients who had gastric radiation injury led to more prompt surgery in the second and third cases. In the last three cases reported, the indication was intractable pain which had not been alleviated by a rather lengthy trial of a rigid medical regime, similar to that for peptic ulcer. Unfortunately, several of these patients had other complications which were noted at the time of operation, particularly small intestinal radiation injury. We now have several cases which have shown ulceration by x-ray and gastroscopically and which have been treated on a medical regime with alleviation of symptoms and a betterment of the general condition which has led us to select only the most severe cases for surgery. The apparent progressiveness of the symptoms and the pathologic condition of the stomachs has led us to the belief that some of these patients may eventually require gastric surgery.

Intensive study of the radiation doses and the tolerance of the stomach and other organs of the gastrointestinal tract in human beings is now in the process of completion.* In the series that is being followed here there is apparently a

*This is being carried on mainly by Lieutenant Colonel Milton Friedman, Chief, Radiation Therapy Section, Walter Reed General Hospital.

very marked individual variation in tolerance to radiation. Quite a few patients who have received 5,000 r. or above to the epigastric region at the level of the eleventh dorsal vertebra have had no gastrointestinal symptoms. On the other hand, ulceration has been noted in patients with much less radiation. The roentgen formula used in these cases was 1000 kilovolts, 3 milliamperes, filter 3 mm. tungsten, and a focal skin distance of 70 or 100 cm., 88 to 40 r. respectively, being delivered per minute.

CASE REPORTS

CASE 1.—C. was 29 years old. In March, 1945, he dropped an oil cooler out of an airplane and in trying to get out of the way, he noted pain in his left side and left testicle. At the time, he felt as if someone had kicked him there and about one week later he noticed that the testicle was becoming hard and enlarged. Because of the enlargement of the left testicle, the patient was hospitalized and applications of ice packs were given. There seemed to be a slight diminution in the size of the testicle and in July, 1945, he returned to duty. However, the testicle continued to become enlarged, although no further pain was noted. He was again admitted to the hospital and after aspiration of the testis with negative laboratory results, he was transferred to Walter Reed General Hospital. Intravenous pyelograms and x-ray studies of the chest and pelvis were negative. The patient received ten x-ray treatments from October 2 to October 15 for a total tumor dose of 1000 r. It was estimated that there was about 20 per cent reduction in size and that the testicle felt softer than it had prior to radiation. On Oct. 18, 1945, radical orchidectomy with resection of the retroperitoneal nodes was done. A number of small nodes were removed from the external iliac and lower portion of the aorta. There was a large fixed ovoid mass 10 cm. long, 5 cm. wide, and 3 cm. deep plastered against the aorta in the midline and fixed to the anterior surface of the vertebral column. The lower border of this mass was at the level of the lower pole of the left kidney and extended proximally for a distance of 10 cm. At the same time, the testicle and spermatic cord were removed. Histologic study of the testicle revealed a teratoma with embryonal adenocarcinoma component, the latter showing moderate to marked radiation effect. The large para-aortic nodes were believed to be metastatic. Irradiation was started and the patient received twenty-four x-ray treatments from Oct. 27 to Nov. 29, 1945. A tumor dose of 6,456 r. in thirty-two days was delivered over the left umbilical and dorsolumbar portals. As a result of this intensive radiation, only a moderate first degree skin erythema was noted. Very little radiation sickness was experienced during this period. The patient was granted a thirty-day furlough following completion of irradiation.

He was re-admitted to the hospital Jan. 4, 1946. He stated that about two weeks previously, in the middle of December, after leaving the hospital, he experienced pain in the lower epigastrium, radiating to the back. Slight relief was noted after drinking ginger ale and orange juice. At night, the pain was intermittent and rather sharp. No relationship to meals was noted. No melena or hematemesis had been noted. With the attacks of pain there was vomiting. Physical examination was not remarkable. Because of the continuance of the abdominal pain, a gastrointestinal series was obtained and this showed the prepyloric region of the stomach to be constricted and funnel-shaped with partially fixed walls. The rugae in this area were enormously enlarged. In the prepyloric region near the pyloric valve, a large ulcer was thought to be present. The duodenum appeared normal. At this time, the patient was transferred to the gastrointestinal service and was placed on a bland diet, amphojel, tincture of belladonna, and phenobarbital. The patient seemed to improve for the first two weeks, although sporadic pains were noted in the lower abdomen. There was no vomiting during the first several weeks on an ulcer regime, but the patient's appetite was very poor and he still felt very weak. Fractional gastric analysis with histamine revealed specimens containing 0, 65, 115, 100, and 65 units of free hydrochloric acid. In the last week of February, the patient started vomiting at least once a day, usually in the afternoon. The

pain that had been described continued. On Feb. 25, 1946, the patient vomited approximately 750 c.c. of bloody material and was given a transfusion because of impending shock. The patient was placed on routine therapy for gastrointestinal hemorrhage with a modified Meulengracht diet and was comfortable until March 1, 1946, at which time he vomited over 1,000 c.c. of bloody material. Blood pressure immediately thereafter was 60/30 and a transfusion with 500 c.c. of blood, which had been kept available on the ward, was immediately given. Another sublethal episode of vomiting occurred ten hours later, necessitating another transfusion. From this time forward, the patient was vomiting blood daily, necessitating daily transfusions of 500 to 1,000 c.c. of whole blood. The situation appeared hopeless and it was agreed that the only possibility of preventing death from hemorrhage was by surgery. Two hours prior to operation of March 5, the patient vomited about 1,000 c.c. of blood and with the transfusion continuing as he was brought to the operating room, laparotomy was performed.

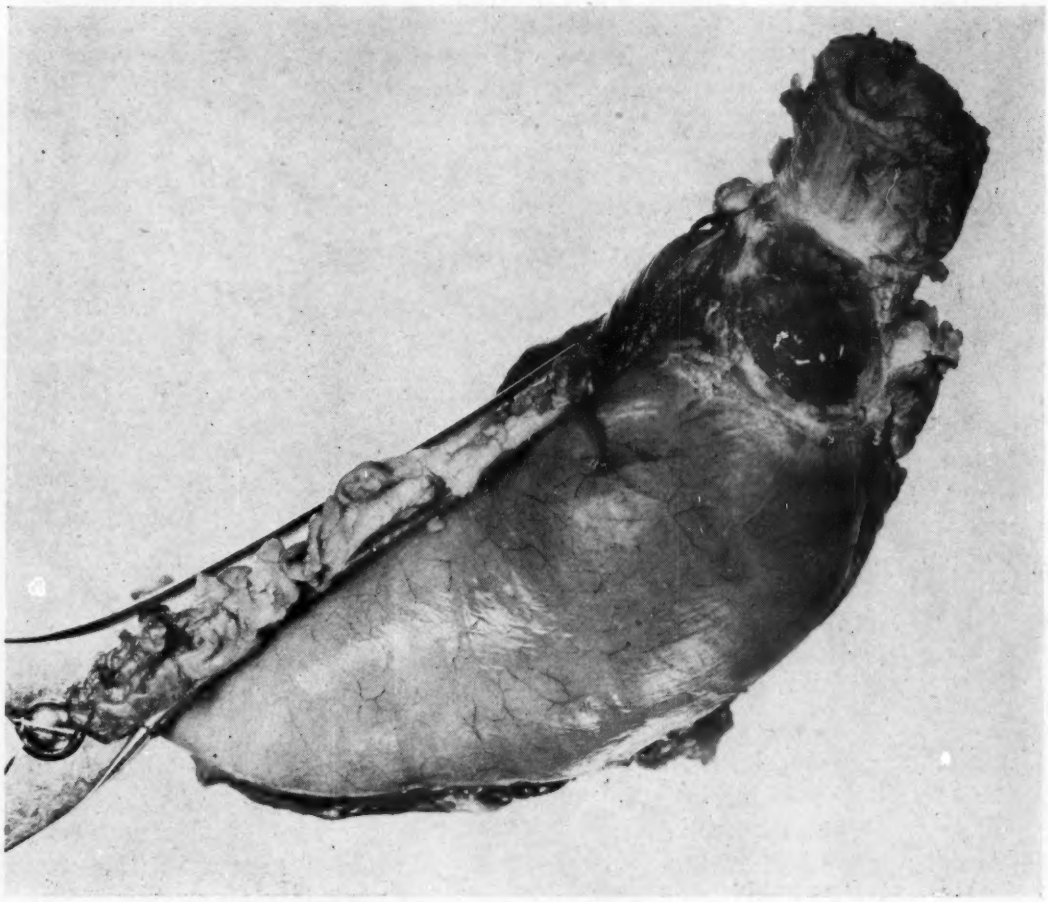

Fig. 1 (Case 1).—Perforation of an ulcer 4 cm. in diameter on the posterior wall of the stomach.

Palpation of the abdominal wall revealed no undue fibrosis or thickening, and no edema or fibrosis of the subcutaneous tissues, fascia, and rectus muscle was noted. After opening the peritoneum, a fibrotic-appearing vascular pylorus was noted. An ulcer about the size of a quarter on the posterior wall of the antral region was noted to have perforated (Fig. 1). In the region of the perforation there was a considerable amount of fibrosis and edema. In the bottom of the pit made by the perforation of the ulcer, there was a large vein which

bled copiously when touched. This was believed to be a branch of the mid-colic vein and after being transfixed, bleeding ceased immediately. The duodenum was cut across about one and one-half inches below the pyloric vein and closed. A gastrojejunostomy was done and an anastomosis was completed. Examination of the transverse colon and other structures lying within the path of irradiation disclosed no evidence of radiation injury to those structures, with the possible exception of one loop of the jejunum which seemed to be somewhat thickened. Palpation of the retroperitoneal area at the site of the node which was noted at the time of the radical dissection of retroperitoneal nodes revealed no evidence of disease. The patient tolerated the operation very well. Whereas he entered the operating room practically in shock, he left it with a blood pressure of 120/70 and a pulse rate of 72.

The postoperative course was very smooth and the patient was eating a soft diet six days after operation. He was on a full ambulatory status three weeks after the operation. At the time of operation, the patient weighed 96 pounds and in the first month postoperatively gained sixteen pounds. There was alleviation of all the patient's symptoms and after six weeks he was able to tolerate a regular diet. The only difficulty occurred from slight drainage from the abdominal wound which continued for several months. Except for the small incisional draining sinus which revealed, on July 5, 1946, suture material, the patient has had no difficulty whatever. At the time of reporting, Aug. 31, 1946, some five months postoperatively, the patient weighed 130 pounds and had no gastrointestinal symptoms. Throughout, monthly chest roentgenograms were taken and have been reported negative. A fractional gastric analysis with histamine done April 13, 1946, more than one month after the operation, showed no free hydrochloric acid. Small intestinal study done April 20 showed a satisfactorily functioning gastrojejunostomy and no changes in the small intestine.

At follow-up examination one year postoperatively, the patient had no symptoms and was well.

Comment.—This patient was one who had a testicular teratoma with embryonal adenocarcinoma component and rather extensive retroperitoneal metastasis on admission to this installation. A tumor dose of 6,456 r. was delivered in thirty-two days, which represents rather massive and thorough irradiation in a comparatively short period of time. Despite this heavy dosage, the patient had only a moderate first degree skin erythema and very little radiation sickness, indicating that his tolerance, at least as far as the skin was concerned, to radiation was very high. In this case, a 10 by 15 cm. portal was used. Thirty-two days after completion of radiation therapy, gastric symptoms began to appear and there was confirmation of gastric changes by x-ray. A medical regime was not very successful in controlling the patient's symptoms. The weakness, anemia, and lack of appetite that the patient had seemed to be a rather typical triad in addition to the gastrointestinal symptoms that are present in all these patients. It is also interesting in view of the widely prevalent belief that radiation depresses the secretion of hydrochloric acid in the stomach,[6] that this patient's gastric analysis with histamine showed several specimens containing over 100 units of free hydrochloric acid. With the onset of hematemesis approximately 2½ months from the onset of the gastrointestinal symptoms, a radical departure in the mode of treatment was indicated. In this patient, the medical attempt to control bleeding, we now agree, was too long and, because of the repeated episodes of bleeding, surgically he was a poor risk. As many authors have indicated, the results of surgery of this type are almost directly correlated with the number of successive attacks of hemorrhage. It was quite fortunate

that at operation the bleeding point was found quickly and tied off immediately. In this case the examining surgeon did not find radiation changes in other parts of the gastrointestinal tract. Of interest, particularly to the radiation therapist, is the fact that the previously noted retroperitoneal metastatic lesion had completely disappeared. The postoperative course in this case was so good that it led to an evaluation of our methods in handling future cases.

CASE 2.—Tr., aged 30 years, was a soldier who enjoyed his usual state of health until March, 1945. At that time overseas he began to complain of low abdominal pain which he described as crampy and occurring chiefly at night. These pains continued to get worse and there was also constant severe low backache. There were no other gastrointestinal symptoms present. The patient returned to the United States and because of the continuation of symptoms sought medical attention. He was admitted to an Army regional hospital on July 26, 1945. During this period of illness the patient felt he had lost ten pounds in weight. A cervical lymph node was biopsied and the pathologic report of papillary adenocarcinoma, metastatic, the site of origin unknown, was returned. Because of this finding, he was transferred to Walter Reed General Hospital on Sept, 20, 1945.

On admission to this hospital, the patient complained only of low midabdominal cramplike pain. Small shotty glands were noted in the left axilla. A firm, hard mass in the midabdomen extending about two inches below the umbilicus and five inches to the left of the midline was noted. This mass was quite tender. Both testicles were noted to be small and atrophic. X-ray studies revealed a large retroperitoneal mass which displaced the colon and both kidneys. The lower poles of both kidneys were rotated anteriorly. A slight degree of gynecomastia was noted one week after admission. From Sept. 28 to Oct. 24, 1945, the patient received thirty x-ray treatments for a total of 3,700 r. to the anterior umbilical portal, 3,700 r. to the posterior abdominal portal, and 4,000 r. to the left side of the neck. Six additional x-ray treatments were given from Nov. 5 to Nov. 10, 1945, for a total dose of 4,900 r. to each of an anterior umbilical and posterior umbilical portal. This made a total tumor dose at the level of the eleventh dorsal vertebra of 5,880 r. in forty-four days with a 15 by 20 cm. portal. During the period of radiation, the patient experienced moderately severe radiation illness with nausea and occasional vomiting. As a result of the radiation, the mass in the abdomen shrunk rapidly and the nodes in the neck disappeared completely.

It was the opinion of the tumor board to which this case was presented that the most likely site of origin was testicular. At the completion of radiation therapy, the patient was granted a thirty-day furlough from which he returned on January 5 feeling fairly well with no particular loss in weight. He did experience some nausea and occasional vomiting which began about forty-five days after the completion of therapy. The patient was granted another furlough. After return from this furlough March 1, 1946, there was noted a small increase in the size of the right testicle. Accordingly, on March 5, 1946, a right orchidectomy was done and histologic study revealed a seminoma. Following this operation, the patient received twenty-two prophylactic x-ray treatments from March 18 to April 16, 1946, for a dosage of 2,500 r. suprapubic, 2,500 r. right anterior chest, 2,000 r. left anterior chest, 2,000 r. right posterior chest, and 2,000 r. left posterior chest. On March 25, 1946, a routine chest roentgenogram revealed the presence of a dense oval mass superimposed on the cardiac shadow which appeared to be due to large mediastinal metastatic nodes that extended into this area from the large retroperitoneal mass. With exhibition of the radiation to the chest portals there was disappearance of the chest shadow within two weeks.

The patient's general condition was good until the first week in April, 1946. At that time there was the onset of vomiting, the vomitus containing clots of blood. At about the same time the patient began to feel weak and had dizzy spells and severe headaches. The vomiting was not accompanied by nausea or pain and was entirely unrelated to meals. The patient did not feel that food precipitated the vomiting. An upper gastrointestinal x-ray series on April 6, 1946, revealed some retention of fluid in the stomach, tenderness

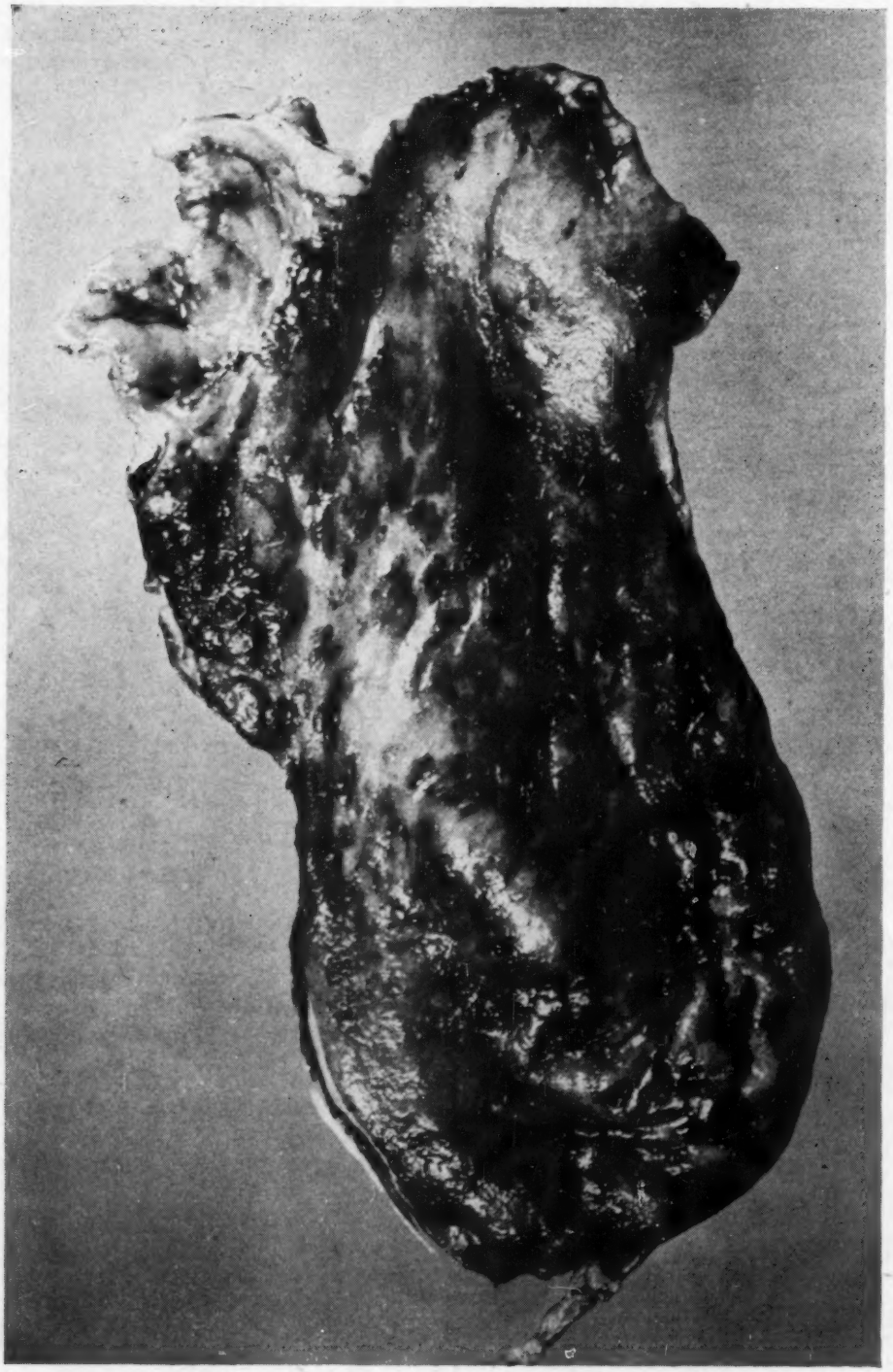

Fig. 2 (Case 2).—Hyperemia of mucosa of stomach with areas of submucosal ecchymosis; the entire wall is thickened and edematous.

over the antrum with narrowing of the stomach in this area, and hypertrophied antral rugae. The duodenal cap was flattened on its superior surface. Prior to the onset of hematemesis, the patient's red count had been adequate, a typical example being that of March 4, 1946, when the red blood cells were 4,150,000 with 85 per cent hemoglobin. On April 15, the patient's red count was 3,600,000, but with the continuance of hematemesis it dropped to 1,930,000 by April 19, despite daily transfusions. The patient also received one to two pints of whole blood daily with a steady drop in the red count. During this period of hematemesis, no pain was complained of by the patient. It was decided, despite the widespread metastatic process, to carry out an exploration on this patient since he was being exsanguinated from the constant loss of blood from the stomach.

At operation, it was noted that the upper two feet of the jejunum were dilated with thickening of the wall and had a peculiar whitish aspect unlike the remainder of the small bowel. The stomach from its upper third downward was thickened, edematous, and seemed to be avascular. The duodenum was noted to be attached to the gall bladder by thick adhesions and these were loosened with a great deal of difficulty. The entire duodenum seemed to be involved in the fibrotic process previously noted in the jejunum. No large ulcer was noted in the stomach. Many oozing points, however, were noted in the edematous nucosa of the stomach. For the anastomosis, a portion of jejunum below the fibrotic area was chosen and this left a very long proximal loop. This had to be done because of the apparent radiation injury to the upper portion of the jejunum. The entire surface of the resected stomach was noted to be hyperemic with multiple patches of hemorrhage and submucosal ecchymosis. The entire wall was thickened and edematous (Fig. 2).

Two days after operation it was noted that the patient's sclerae were yellow and by April 28 the skin was definitely icteric. No vomiting or nausea was noted for the first two weeks. Seven days postoperatively a fecal fistula developed at the site of the operative wound and it was felt that this probably arose from the long loop of jejunum which showed marked radiation effect at operation. The patient's condition deteriorated progressively with jaundice, fecal fistula, inability to eat, and occasional elevation of temperature. The patient was given supportive therapy by intravenous feedings and transfusions. Despite that therapy, emaciation continued progressively and the condition of the patient by June 1, 1946, was very poor. In the middle of June, 1946, it was noted that ingested food occasionally came out of the fistula in the abdominal wound which was about 15 cm. in diameter and 1 cm. deep. The patient continued to get weaker and died June 29, 1946.

Comment.—This patient was admitted with rather widespread metastatic disease. The glands were present in the axilla and neck and there was a large retroperitoneal mass in the midabdomen which displaced the colon and both kidneys. The testicles were noted to be small and atrophic, but in the experience at this installation, this fact does not rule out primary testicular tumor in any metastatic disease, particularly when there is retroperitoneal metastasis. At any rate, the patient received 5,880 r. in forty-four days with a 15 by 20 cm. portal. Moderately severe radiation illness was noted during treatment. There was noted shrinkage in the abdominal mass and six months after admission to this hospital a small increase in the size of the right testicle was noted which led to a right orchidectomy. Histologic diagnosis of testicular seminoma was then made. In addition to the metastases already mentioned, mediastinal metastatic involvement was noted six months after admission and treated with radiation with disappearance of the chest shadow. It will be noted that the patient received a large dosage of x-ray to the abdomen in a relatively short period of time. The onset of the gastrointestinal symptoms began about forty-five days after

completion of therapy but was not very severe and did not require rigid ulcer regime. The gastrointestinal condition became serious approximately five months after the completion of radiation therapy when bloody vomitus was noted. There was no nausea or pain with the vomiting and clots of blood were noted in the vomitus. At no time was there massive hematemesis as was noted in the first case. It was postulated that the patient was probably having oozing from a bleeding ulcer. In this case where the metastatic process was so widespread there was some doubt as to the wisdom of abdominal operation but it was felt that the continuing loss of blood from the stomach would probably terminate in a fatality from that source unless something was done. Medical treatment was attempted and was of no avail. At operation, unfortunately, marked involvement of a good portion of the jejunum was noted despite which fact subtotal resection was done. The gross appearance on opening the stomach was that of ecchymosis and multiple patches of hemorrhage. The entire wall was thickened and edematous. In this case the patient did poorly because of the development of a fecal fistula at the site of the operative wound which probably arose from the long loop of jejunum that had shown such marked radiation effect at operation. The patient lived more than two months after the operation and in view of the widespread metastases, as well as the widespread injury to the small bowel, complicated by the active bleeding from the stomach, it is felt that the operation was a temporary lifesaving procedure in a hopeless situation.

CASE 3.—H., aged 30 years, on March 1, 1946, noted swelling of the left testicle with no pain. The soldier was hospitalized and prostatic smears were reported to have shown acid-fast bacilli. However, after a course of penicillin and sulfonamides he was returned to duty with a diagnosis of nonspecific epididymitis. Because of the continuance of the swelling, the patient was again hospitalized overseas and on the basis of laboratory findings, evacuated to the United States with the diagnosis of tuberculous epididymitis on the left. Nine days after arrival in the United States, a left orchidectomy was performed and a histologic diagnosis of embryonal carcinoma was made. The patient was transferred to Walter Reed General Hospital on Sept. 22, 1945, for further therapy.

On Oct. 2, 1945, a radical resection of the retroperitoneal nodes and spermatic vessels on the left side was done. Under anesthesia, abdominal palpation revealed a large mass extending from the level of the umbilicus upward toward the left kidney. A large metastatic mass which had produced deviation of the left ureter on intravenous pyelography was noted to involve the ureteral wall and it was deemed necessary to perform a nephroureterectomy in addition to the removal of the large metastatic mass. Although the mass stripped off the aorta with ease, the fascia over the psoas muscle had become involved and in the mass the left renal vein was noted to be involved. Histologic examination of the removed metastatic mass revealed embryonal carcinoma. The patient withstood the operation without any complication.

From October 17 to December 11, the patient received forty-five x-ray treatments; 5,200 r. were given to each of the following portals: dorsolumbar, left suprapubic, umbilical, epigastric, lumbodorsal. This is a tumor dose of 5304 r. at the level of the eleventh dorsal vertebra in fifty-five days. During the period of radiation, the patient had severe radiation sickness consisting of nausea and vomiting, but at the completion of treatment, began to improve. Weight increased from 131 to 140 pounds in the first three weeks after radiation therapy and no vomiting or abdominal pain was noted. The improvement continued until the middle of January, 1946, when he noticed epigastric pain followed in a few days by vomiting, particularly in the morning. Night pain was also persistent. The pain came on

usually two to three hours after eating and medication with belladonna and phenobarbital with frequent milk feeding seemed to afford some relief. Because of the extensive retroperitoneal metastasis, it was decided to give prophylactic irradiation to the mediastinum and left supraclavicular area. Accordingly, the patient received twenty x-ray treatments from Feb. 27 to March 26, 1946, with a total dose of 2,000 r. to each of four portals over the thoracic cage. He also received five x-ray treatments with a total dose of 2,000 r. from Feb. 27 to March 6, 1946, over the left supraclavicular area.

The patient stated that during this time there was also some overlapping of the radiation into the epigastric region. In the middle of March during the radiation he had violent radiation sickness and vomited several times a day. There was loss of appetite and a constant dull epigastric ache. The patient complained of passing a great deal of flatus both orally and by rectum. During this period, however, the vomitus was bile-tinged and there was no blood or coffee-grounds material noted. An upper gastrointestinal series done in January, 1946, revealed no pathology.

After the completion of the chest and supraclavicular radiation, the patient was granted a furlough and he felt fairly well for the first two weeks. Beginning in the first week of April 1946, a dull ache in the epigastrium was noted and again there was some vomiting. At this time the vomitus seemed markedly changed. It was usually dark brown in color and on one occasion bright red blood was noted. On April 20, the patient began to suffer with severe epigastric pain occurring two to three hours after eating and somewhat relieved by frequent milk feedings. During the next week, although the vomiting became less frequent, occurring every three to four days, the vomitus had a rich brown coloration. The stools were hard and dark brown. He was seen by a doctor in his home town who placed him on a soft diet with amphojel medication. However, the vomiting continued and there were sharp pains in the epigastrium which radiated to the right upper quadrant. In the first week of May, 1946, the patient noted marked weakness, anorexia, shortness of breath on the slightest exertion, palpitations of the heart, and fading images described as "blackout." Because of the weakness, the patient returned from furlough and physical examination revealed a markedly anemic, fatigued individual with marked pallor of all mucous membranes. Some tenderness on palpation of the epigastrium and in the upper right rectus region was obtained. Red blood cells were 2,100,000 with 5.89 Gm. (38 per cent) of hemoglobin. The patient was given daily transfusions and placed on a rigid ulcer regime. An upper gastrointestinal x-ray study on May 10 revealed marked narrowing of the antral portion of the stomach, and a spastic duodenum. No definite ulcer crater was demonstrated. Despite adequate medical treatment, the patient continued to vomit sporadically, the vomitus containing bright red blood.

Accordingly, the patient was prepared for surgery which was performed on May 14, 1946. At operation there was some fibrosis and edema in the abdominal musculature and there was more vascularity than is normally seen. The small intestine appeared normal except for slight thickening of a loop or two of the upper jejunum. The stomach in the region of the pylorus was greatly thickened, edematous, and had a whitish appearance. The liver appeared to be normal. A subtotal resection and a gastrojejunostomy were performed. On opening the stomach just proximal to the pyloric ring, an irregular ulcer 2 cm. in diameter and 2 mm. deep, appearing to reach to the muscularis, was seen (Fig. 3). In the pyloric portion of the stomach, the rugae appeared to be flattened and the mucosa appeared to be somewhat thickened and edematous with occasional small petechial hemorrhages. Microscopically, the mucosa exhibited moderate atrophic changes and evidence of edema. The most marked changes were seen in the submucosa, which was very edematous, with an increase of connective tissue elements and a mild increase in vascularity. The pathologists noted that the ulcer and stomach in general show a striking contrast to the usual gastric ulcer in that the mucosa in this case is atrophic, whereas in the ordinary gastric ulcer it is most often hyperplastic. The patient tolerated the operation fairly well and the postoperative course was without incident. There was cessation of vomiting and epigastric pain. However, three weeks postoperatively the patient began to complain of abdominal

cramps with occasional diarrhea and poor appetite. He also complained of abdominal distention and the passage of a great deal of flatus by rectum. An upper gastrointestinal x-ray study was performed June 13, 1946, and a small ulcer niche in the anterolateral wall of the stoma was noted. There was some delay in the emptying time as a small residual of barium was noted at three hours in the stomach. However, at six hours, the stomach was empty. The mucosal pattern of the ileum was distorted, the walls being thickened and relatively fixed. The passage of barium through the small bowel was delayed and the meal had not reached the cecum in six hours. It was felt that there were changes in the small bowel, probably a result of radiation. Although the patient's appetite has improved and he has gained weight, physical examination shows marked distention of the abdomen, but no fluid is believed present. Occasional enemas relieve the distention for only a short period.

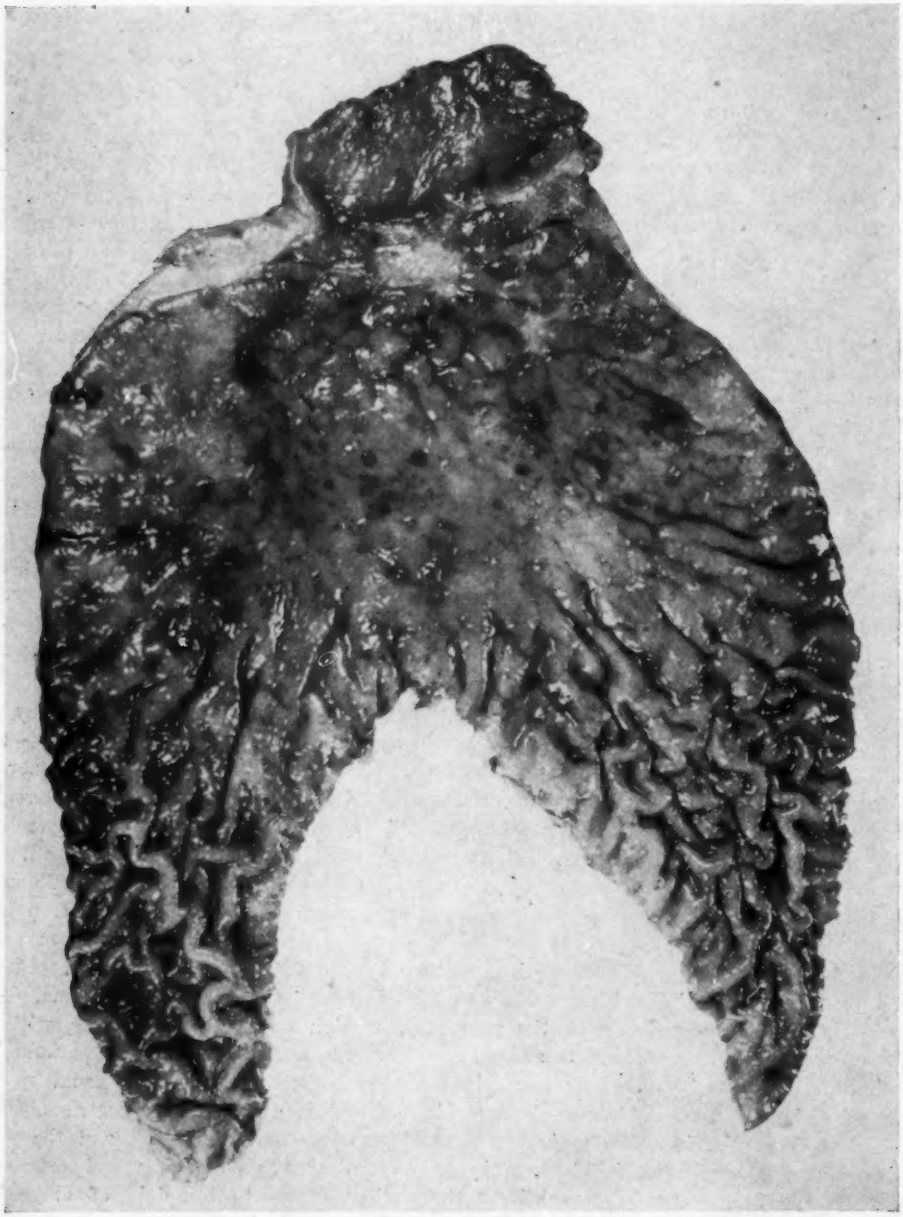

Fig. 3 (Case 3).—A large irregular ulcer is seen proximal to the pyloric ring; in the antrum there are areas of petechial hemorrhage and the wall is thickened.

Comment.—This patient had an embryonal carcinoma of the testis with a large retroperitoneal metastatic mass. He received a tumor dose of 5,304 r. in fifty-five days with a 10 by 10 cm. portal. During radiation, the patient had severe radiation sickness but there was improvement on completion. Gastrointestinal symptoms did not begin until thirty-five days after completion of therapy. Additional radiation was given to the mediastinum prophylactically and there was some overlapping of the thoracic radiation onto the epigastrium. However, at the time the patient first complained of epigastric discomfort, a gastrointestinal series did not reveal any pathology. It was not until four months later that the patient had severe epigastric distress with occasional bouts of vomiting. During this period the vomitus contained some blood. Four months after completion of the first course of radiation therapy, hematemesis was noted with marked weakness and loss of blood. At operation, some fibrosis, presumed due to radiation, was noted in the upper jejunum. The stomach revealed an ulcer in the pyloric region and petechial hemorrhages throughout the mucosa of the antrum. The postoperative course was uncomplicated for the first three weeks. At that time, complaints of abdominal cramps with occasional diarrhea and anorexia were noted. X-ray studies revealed a small ulcer niche in the stoma. In summary, we have been dealing with a case of widespread metastasis in which the prognosis from the start was very poor. Complications that have developed postoperatively were not a result of the operation which in this case, too, was a lifesaving procedure.

CASE 4.—Y., aged 29 years, was in his usual state of good health until about April, 1945, when he noticed pain in the midabdomen accompanied by nausea. About the same time, swelling in the right scrotum, together with hardness and enlargement of the right testicle, was noted. Although there were no chills or fever, the scrotum became warm and red. The pain in the scrotum became progressively worse and the patient was hospitalized overseas where he was treated with a suspensory and prostatic massage. Early in May, 1945, a slightly tender swelling was noted in the right inguinal region. The pain continued for the next two months and the patient was evacuated to the United States on Aug. 31, 1945. He arrived at Walter Reed General Hospital Sept. 28, 1945.

Physical examination on admission to this installation revealed a large globular irregular hard mass the size of an orange in the right scrotum. A fixed mass was also felt in the left lower abdomen extending from the left inguinal region to the umbilicus. A test dose of 500 r. to the right testis and 400 r. to the right inguinal node was given and there was shrinkage in the size of the right testicle of about 65 per cent and of the right inguinal nodes of about 85 per cent in one week. On Oct. 25, 1945, right orchidectomy with excision of the right external inguinal nodes was performed. The histologic examination of the testicle revealed an embryonal carcinoma which showed marked radiation effect. Following the operation, radiation therapy was continued and the patient received thirty-six x-ray treatments from Oct. 3 to Nov. 20, 1945 with a 15 by 20 cm. portal over the anterior and posterior abdomen for a dosage each of 5,500 r. This represented a tumor dose of 6,105 r. in forty-nine days at the level of the eleventh dorsal vertebra. At the completion of radiation therapy, abdominal examination did not reveal the retroperitoneal mass previously palpated. The patient was granted a furlough and on return from the furlough complained of no symptoms. By the end of January, 1946, the patient's general condition was good, weight was 156 pounds, and no complaints referable to the upper gastrointestinal tract were present, despite the tumor dose of 6,100 r. to the center of the epigastrium. Prophylactic radiation was given to the mediastinum and left supraclavicular region, the patient receiving

fourteen x-ray treatments from Jan. 10 to Jan. 24, 1946, for a total dosage of 2,000 r. to the suprapubic area, 1,500 r. to both anterior and posterior mediastinal areas, and 1,200 r. to the left supraclavicular area. Following this therapy the patient was granted another furlough.

While on furlough during February and March, 1946, the patient continued to gain weight and early in March weighed about 175 pounds, which was normal for him. About March 15, however, he began to notice pain in the epigastrium which he described as burning in type and being located over the entire epigastrium. This interval was four months after the last treatment to the abdomen and two and one-half months after the last treatment to the mediastinum and suprapubic area. The patient did not notice any relationship to meals. The pain occurred sporadically and was usually accompanied by nausea and vomiting which afforded some relief. Night pain occurred frequently, accompanied by vomiting. There was no blood or coffee-grounds material noted in the vomitus. Tarry stools were not present. With the onset of the epigastric pain, his appetite became very poor and on return from furlough the patient had lost ten pounds. A gastrointestinal series done April 6, 1946, revealed marked narrowing of the stomach in the antral region. A filling defect was noted 3 cm. proximal to the pyloric sphincter with a crater measuring 5 mm. in diameter and 2 mm. deep. Some hypertrophy of the valvulae conniventes was noted. The patient was placed on an ulcer regime and for the first month on the ward of the gastrointestinal section the patient seemed to improve. Sporadic attacks of excruciating mid-epigastric pain occurred. Gastroscopy on April 18, 1946, revealed reflux of bile from the duodenum with a patulous pylorus and a rigid antrum. Fractional gastric analysis on April 6, 1946, with Ewald meal revealed specimens of free hydrochloric acid of 11, 22, 49, 80 and 38 units. Repeat fractional gastric analysis with histamine on May 4, 1946, revealed specimens of free hydrochloric acid of 0, 0, 45, 72, and 46. Examination of the stools revealed occasional one to two plus occult blood. For the next month the patient's symptoms continued to get worse with intermittent attacks of epigastric pain and occasional vomiting. There was very little loss in weight, however, and no evidence of further metastasis of the primary disease. Repeat upper gastrointestinal study revealed an ulcer 3 by 2 cm. in the distal portion of the antrum on the posterior wall. Because of the continuing pain which required moderate amounts of narcotics to control, and in view of the x-ray findings, it was felt that the patient was probably having or had had a perforation of the antral ulcer. During this whole period of time there was no hematemesis noted and the patient had a comparatively normal blood picture. Hematocrit on May 21 was 37 volumes per cent and blood count on May 25 was 4,050,000 red cells with 81 per cent hemoglobin.

On May 26, 1946, laparotomy was performed. The liver appeared to be somewhat smaller than normal. The stomach was seen to be edematous and vascular, and just above the pylorus an indurated area with a crater was felt on the posterior wall. The upper two feet of the jejunum were noted to be whitish, thickened, and edematous. It was felt that the duodenum was free enough of radiation injury to justify resection. On following the stomach posteriorly, a perforation of the posterior wall of the stomach into the pancreas and tranverse mesocolon was encountered (Fig. 4). A subtotal gastrectomy and gastrojejunostomy were performed. The jejunum selected for the anastomosis was below the fibrotic area previously described. The patient's immediate postoperative course was uneventful and one month after operation the patient was transferred back to the gastrointestinal section for further care. At the end of June, 1946, the patient was asymptomatic and ambulatory with complete relief of the preoperative symptoms.

However, in the second week of July, 1946, the patient started to complain of periodic generalized abdominal pains, particularly below the umbilicus. There was a slow weight gain and his appetite remained good, but the pains in the lower abdomen have continued to the time of this writing. There has been no evidence of bleeding. The patient also complains of distention and flatus and is having two bowel movements, not particularly

loose, daily. X-ray studies of the upper gastrointestinal tract revealed a normally functioning posterior gastroenterostomy with no evidence of stomal ulcer. Mucosal pattern of the small bowel appeared normal. However, barium enema performed July 24, 1946, revealed an area approximately 12 cm. in length in the mid-portion of the transverse colon which is noted to be irritable, spastic, with mucosa that appears to be ulcerated. At the time of writing, the lower abdominal symptoms continue.

At follow-up examination one year postoperatively, the patient was fairly well with occasional lower abdominal pain relative to a colitis secondary to radiation.

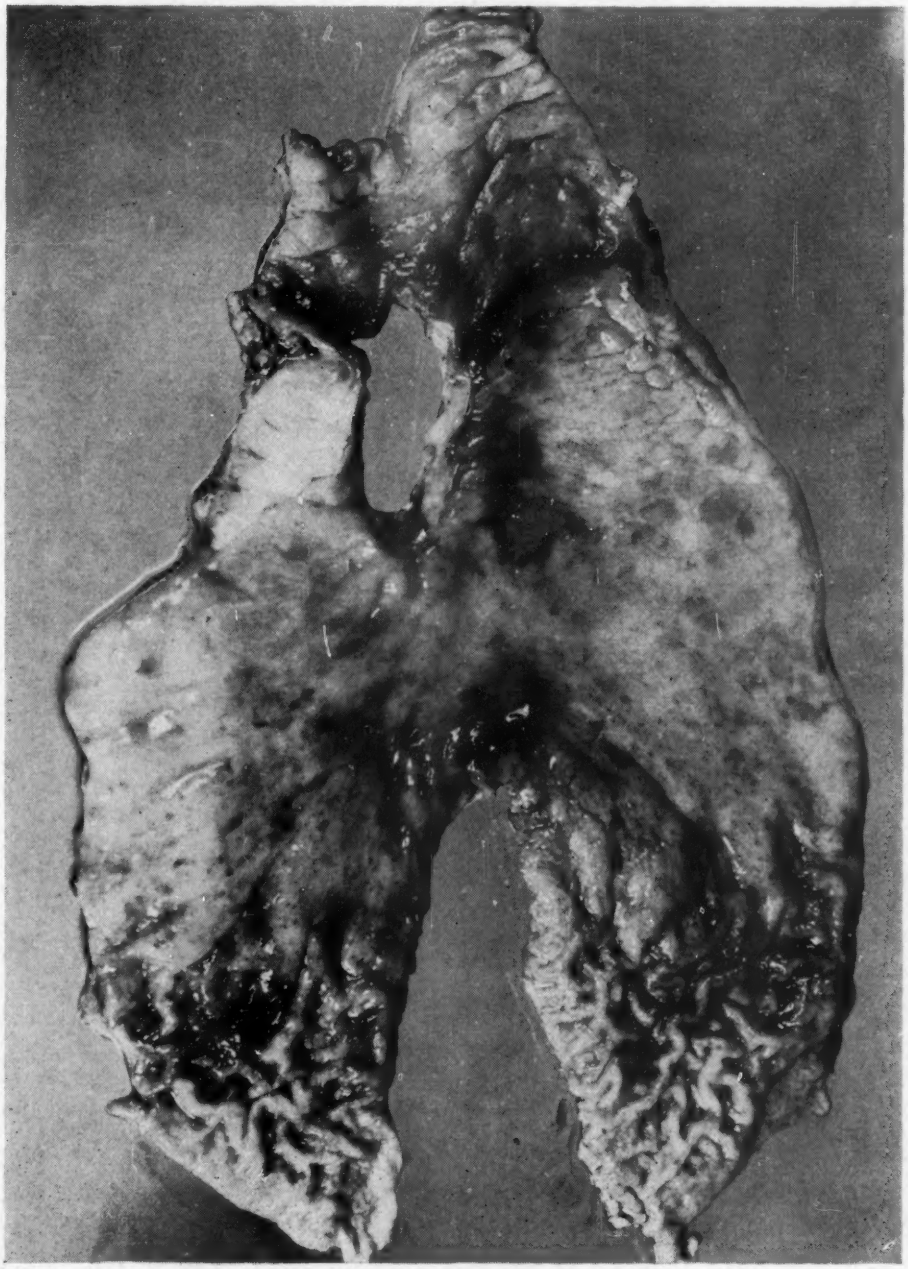

Fig. 4 (Case 4).—Perforation of the posterior wall of the stomach.

Comment.—This patient had an embryonal carcinoma of the testicle with right inguinal and retroperitoneal nodal metastasis. He was given a tumor dose of 6,105 r. in forty-nine days with a 15 by 20 cm. portal, at the completion of which time abdominal examination did not reveal the retroperitoneal mass previously palpated. Additional radiation was given to the mediastinum and left supraclavicular area. Gastrointestinal symptoms began about four months after the completion of radiation to the epigastrium. In this case, medical treatment was not successful in relieving the pain and the marked loss of appetite that the patient had. In view of the excruciating attacks of pain and the vomiting which occurred during these episodes, it was felt that the possibility of perforation having taken place was a good one. In this case, no bleeding occurred prior to operation, but it was felt that operation was indicated because of the terrific pain and discomfort that the patient had. Impression of perforation was confirmed at operation and it was noted that the upper two feet of the jejunum were probably also affected by the radiation. It is well to note that the portal used in this case was rather large and covered a larger area than some of the other cases. The postoperative course was good and for the first month the patient was asymptomatic with complete relief of preoperative symptoms. One and one-half months after operation, however, the onset of lower abdominal pain was noted with distention and flatus and slight diarrhea. A barium enema revealed the mid-portion of the transverse colon to be ulcerated, probably the result, too, of radiation. The indication for this operation was the perforation and the lack of relief of symptoms obtained by medication.

CASE 5.—B., aged 25 years, was in his usual state of health until June, 1945, when, while playing baseball, he injured his left hip. Two days later, swelling of the left scrotum was noted. The patient was seen on sick call and treated but was returned to duty in four days. However, the swelling continued and he was finally hospitalized in September, 1945, at which time a left orchidectomy was performed. Histologic diagnosis of carcinoma was made postoperatively. The patient was evacuated to the United States and admitted to this hospital Oct. 21, 1945.

It was decided to treat this patient with radiation and this was begun on Oct. 26, 1945. From that date until Dec. 20, 1945, the patient received forty-five x-ray treatments, 5,200 r. being given to the following portals: Left suprapubic, umbilical, epigastric, lumbosacral, lower dorsal. This delivered a tumor dose of 5,096 r. at the level of the eleventh dorsal vertebra in fifty-four days. Radiation sickness during the period of treatment was moderately severe with generalized abdominal pains, nausea, and occasional vomiting. Although his appetite was poor, weight remained stationary. Because of the severe radiation sickness and the awareness at that time of the possibility of gastric injury, an upper gastrointestinal radiograph was obtained and was reported to be negative. Treatment was, therefore, continued and he finished the radiation in good general condition. The patient was granted a furlough at the completion of therapy and on return stated that he had felt fairly well in the past month. However, he complained of epigastric distress which was relieved somewhat by food. At that time there was no vomiting, but there had been occasional attacks of nausea with pain which was localized to the mid-epigastrium without radiation. The patient denied ever having had any symptoms referable to the gastrointestinal tract prior to the onset of radiation therapy. Because of the continuing abdominal complaints, a gastrointestinal series was obtained on January 30 and was reported to be negative. For the next two months, the patient continued to complain of epigastric discomfort. The

patient's weight was maintained at 145 pounds and another upper gastrointestinal tract series was obtained. On this examination of March 13, hypertrophy of the mucous membrane of the antral portion of the stomach was noted and there was a suggestion of a possible area of ulceration of the greater curvature in the antral portion. However, no crater could be demonstrated. In view of the symptomatology and the x-ray findings, the patient was transferred to the gastrointestinal section, April 23, 1946.

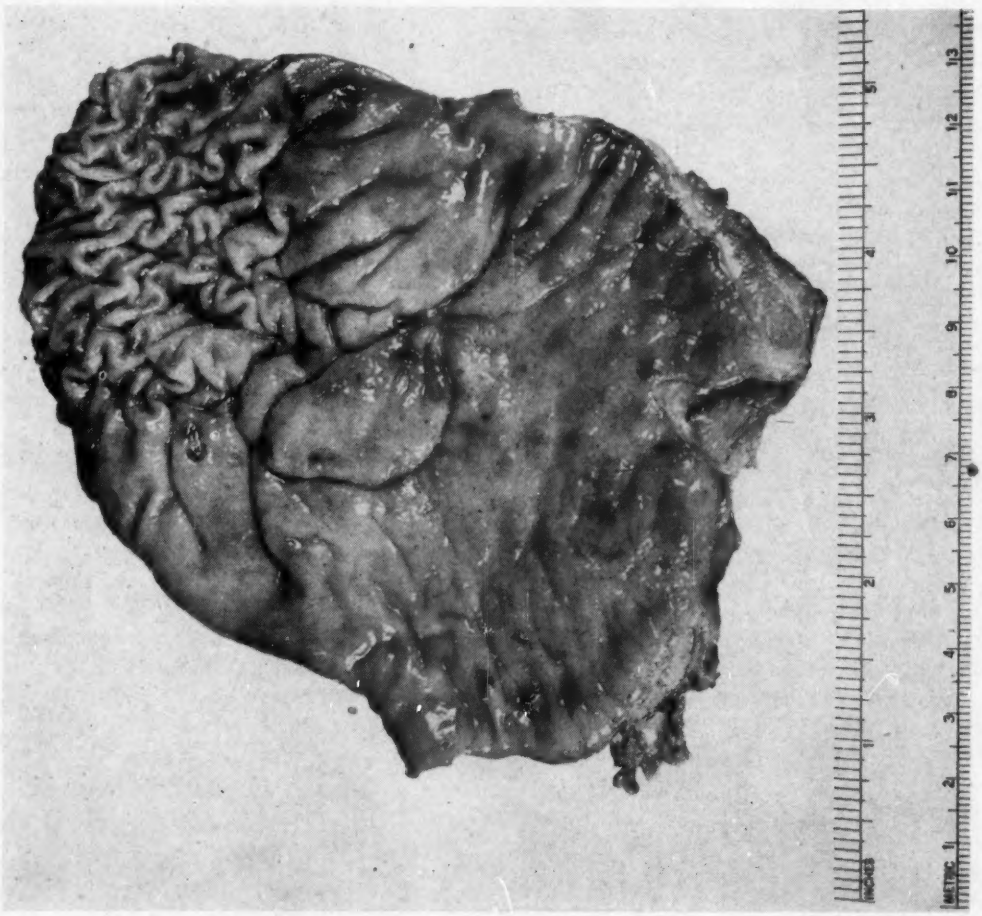

Fig. 5 (Case 5).—Ulcer found in the pyloric ring; mucous membrane is thickened and edematous.

The patient complained of pain in the epigastrium which came on three to four hours after eating. The pain was relieved by eating and milk seemed to afford a good deal of comfort. Occasional attacks of nausea and night pain were also noted. Fractional gastric analysis with histamine on March 27, 1946, revealed specimens containing 0, 0, 77, 55, and 52 units of free hydrochloric acid. Gastroscopy performed April 28, 1946, revealed a rigid antrum but no ulcerations were noted. Repeat gastrointestinal series on April 20 showed, in addition to the narrowing in the antrum, a contracted and irregular duodenal cap. The patient was placed on a rigid ulcer regime and for the first several weeks there seemed to be some improvement in the patient's symptoms. However, there were sporadic attacks of severe epigastric pain which increased in frequency by the middle of May, 1946. At this time, the attacks of pain were accompanied by vomiting and on several occasions, small amounts of bloody material were noted in the vomitus. The patient had days during which he experienced little pain and vomiting and other days during which there were many attacks

of pain and vomiting. It was felt that the patient was showing little improvement on a medical regime and a radiographic study on May 24, 1946, showed progressing changes in the antrum and in the duodenum. It was thought that ulceration was present in the pyloric region, although a definite niche was not demonstrated. Stool examinations were noted to contain occult blood on several occasions. By the middle of June, 1946, the patient was having excruciating pain and attacks of vomiting during which small quantities of fresh blood were noted in the vomitus.

Because of the apparently progressing nature of the disease, it was felt that subtotal gastrectomy was indicated before further complications, such as massive hemorrage or perforation, made themselves evident. Accordingly, the operation was performed on June 27, 1946.* At operation there was evidence of increased fibrosis and alteration in the color of the stomach. Slight changes believed to be due to radiation fibrosis were also noted in the jejunum and transverse colon. In the right flank a serosanguineous exudate which had the appearance of thin watery pus was found. However, no abscesses could be found and examination of the stomach did not reveal grossly a perforation. The antrum of the resected portion of the stomach showed petechial hemorrhages throughout. The mucous membrane was noted to be greatly thickened and extremely edematous. In the pyloric ring just posterior to the lesser curvature, an ulcer 1.8 by 1.7 cm. was noted. This ulcer was approximately 0.6 cm. deep (Fig. 5). It was felt that the edema surrounding the pyloric ring must have practically occluded the lumen of the pylorus. Histologic picture was similar to that found in other stomachs altered by radiation.

Following the operation, the patient did well until the mid-part of July, when he began to have episodes of nausea and vomiting. The vomiting came on at irregular periods and on one occasion 1,300 c.c. of retained gastric contents were aspirated. Because of the continuance of vomiting, barium study was performed and it showed no evidence of a stomal ulcer. A normally functioning gastroenterostomy was noted as well as moderate hypertrophy of the mucosal markings and thickening of the walls of the distal ileum. The patient was transferred back to the gastrointestinal section and has had continuing episodes of nausea and vomiting which come on at irregular periods and in no definite pattern. Despite these attacks of nausea and vomiting, the patient has been completely relieved of the excruciating pains that he had with the attacks prior to operation. It is discouraging to note, however, that small intestinal changes have already appeared by x-ray.

Comment.—This patient had a carcinoma of the testis, and after orchidectomy overseas was transferred to this installation. He received a tumor dose of 5,096 r. at the level of the eleventh dorsal vertebra in fifty-four days with a 10 by 10 cm. portal. During radiation he experienced moderately severe radiation illness. During the period of these symptoms an upper gastrointestinal study was negative. About thirty days after completion of treatment, another gastrointestinal series was obtained and again a negative report was received. However, the patient continued to complain of epigastric discomfort which was rather mild, but became increasingly severe. X-ray changes were first noted three and one-half months after completion of therapy. This patient had sporadic attacks of epigastric pain with nausea and vomiting that continued despite rigid medical treatment for two months. During this period there were also progressive changes by x-ray and the patient's appetite was becoming poorer with concomitant loss of weight. Although it was not felt that any complications were present, operation seemed indicated because of the progressive nature of the patient's condition and because by this time it was felt that such cases of radia-

*Surgery performed by Lieutenant Colonel Frank E. Hamilton, Walter Reed General Hospital.

tion injury that did not respond fairly promptly to medical treatment would probably not respond at any time to medical treatment and surgery was indicated prior to the onset of complications. At operation only slight changes were noted in the jejunum and transverse colon. An ulcer in the pyloric region was revealed on opening the stomach. That the postoperative course would not be uncomplicated is indicated by the small intestinal changes that have already made their appearance by radiologic examination.

CASE 6.—Ty., a 22-year-old white soldier, was in his usual state of health until February, 1945, when he noted that the left testis was harder and larger than usual. There was no pain or history of injury. In August, 1945, the left testicle which had now grown larger was diagnosed as a tumor and the patient was evacuated to the United States. He was admitted to Walter Reed General Hospital, Sept. 29, 1945.

Physical examination was negative except for a hard, heavy, irregular, nontender left testicle slightly larger than normal. On Oct. 9, 1945, a radical left orchidectomy was performed and no metastases were found in the retroperitoneal nodes. Histologic diagnosis of the testicular tumor was teratoma mixed type (teratocarcinoma). This operation was complicated by an incisional abscess which was treated by incision, drainage, and penicillin. When this had healed, the patient was started on prophylactic irradiation and he received 4,800 r. at the level of the eleventh dorsal vertebra from Nov. 12, 1945, to Jan. 4, 1946, in fifty-three days.

During radiation the patient had very little difficulty. About six days after the completion of treatment, he had many gastrointestinal complaints: pain, belching, nausea, and occasional vomiting. These complaints were continuous and persistent. The patient would describe the pain as being severe and cramplike, coming on during the night when the stomach was empty. Occasional relief was obtained by food. Ice cream was well tolerated and relieved the pain, whereas milk or cream caused nausea. Because of these complaints, on Jan. 28, 1946, twenty-four days after completion of therapy, an upper gastrointestinal series was obtained and showed no evidence of an organic lesion of the esophagus, stomach, duodenum, or small intestine. However, the patient continued to complain of epigastric pain and sporadic attacks of vomiting. Because of the persistent continuing complaints, he was transferred to the gastrointestinal section. A repeat x-ray series on February 28 revealed marked changes in the stomach since the previous radiographic examination. The antral mucosal folds were distorted and thickened. A deformity simulating an ulcer crater was noted in the antrum and the duodenal cap showed evidence of disease without ulceration. The patient was placed on a strict ulcer regime with supplemental analgesic medication and began to do fairly well with the exception of occasional epigastric pain. On March 2, 1946, fractional gastric analysis with histamine revealed no free hydrochloric acid in all specimens. The blood counts and hematocrit remained normal until the latter part of March, when a slight drop in the red count was noted. A repeat gastric analysis on March 16 showed specimens containing 0, 0, 35, 25, and 20 units of free hydrochloric acid. The episodes of occasional sporadic epigastric pain continued and about April 1, specimens of the feces showed occult blood at rather frequent examinations. A repeat upper gastrointestinal series on May 3, 1946, showed continuation of the process that had been noticed on previous x-ray examinations of the stomach. In the latter part of April and early May, there was continual progression of the anemia which required transfusions. On May 28, 1946, the patient suddenly fainted on the ward and it was noted that he was very pale; the blood count was 2,300,000 with a hematocrit of 23. The patient had been having three to four loose bowel movements for three days prior to the episode of syncope and it was felt that the bleeding was coming from the ulcer noted by x-ray in the stomach. The episodes of pain remained to a lesser degree during this period.

Gastroscopic examination April 13 showed a rigid, stiff antrum but no ulceration could be noted. The pylorus was noted to be patent and there was reflux bile noted which obstructed the view of the mucosa in the antrum.

On June 12, a left supraclavicular nodal enlargement was noted which was shown by biopsy to be metastatic teratoma. To this area the patient received 2,700 r. in nine treatments from June 14, 1946, to June 29, 1946, with shrinkage of the left supraclavicular nodes. There was continuous bleeding through the lower bowel, necessitating repeated transfusions to relieve the anemia. The pain continued intermittently but was not as severe as it was in the early stages of the gastric disease. Repeat x-ray on June 19, 1946, revealed a 2 cm. ulcer on the greater curvature side of the antrum. A patulous pylorus was noted and the distal half of the body of the stomach and antrum were narrow and fixed with atrophic rugae.

In the latter part of July, the patient noted a tender area in the left upper epigastrium which over a two-week period became very tender and painful to palpation. Physical examination revealed a small tender mass in this area. In view of the fact that this patient was bleeding to the extent that he needed one to two transfusions of whole blood weekly for some time, and in view of the fact that an ulcer was demonstrated by x-ray, it was felt that this mass could well represent a walled-off abscess, secondary to perforation of the ulcer. In view of the constant and continuing blood loss in the past several months without any alleviation by a medical regime, and because of the recent development of the left epigastric mass, it was felt that surgery was indicated without delay.* On Aug. 15, 1946, the patient was operated upon and on opening the free peritoneal cavity, there was found purulent material in the lesser omental sac and the stomach was noted to be bound down in a mass of adhesions which existed between the transverse colon and the duodenum. There was a small walled-off abscess between the posterior wall of the stomach and the transverse colon which was separated with difficulty. Marked adhesions were noted on the serosal surface of the stomach in the greater curvature area. It was also noted at operation that a good portion of the jejunum was involved in the radiation fibrosis and it was with some difficulty that a portion sufficient for anastomosis was found. A partial resection of the stomach was done and a portion of the first part of the duodenum was removed. On opening the resected specimen, there was a 3 by 2 by 3 cm. triangular ulceration on the greater curvature posterior wall of the stomach. The ulcer was about 6 mm. deep and had a hard fibrotic base. In the middle of it there was a smaller deeper area 1 by 0.5 cm. through which apparently the perforation had occurred, although there was no obvious perforation noted since the serosal surface had been completely walled off by adhesions.

Comment.—This patient had metastatic disease for which 4,800 r. were given at the level of the eleventh dorsal vertebra in fifty-three days. Symptoms were noted quite some time before x-ray changes developed. Despite the presence of anemia and blood in the feces, a medical regime was carried on for a long while. The development of an epigastric mass indicated that a new complication of the ulcer had appeared. Operation performed 223 days after completion of radiation revealed peritonitis secondary to a subacute perforation of a large antral ulcer. The patient's postoperative course has thus far been uncomplicated.

SURGICAL OBSERVATIONS

The indications for surgery in this group of cases differ little from the indications for surgery in peptic ulcer. Perforation, hemorrhage, and intractability of symptoms have been the indications in the series presented. Possibly, surgical intervention at an earlier period is indicated in those cases of ulcer secondary to radiation that do not respond rather quickly to a medical regime. In proportion to the number of cases observed, the complications occur in greater proportion than in ordinary peptic ulcer. The well-known fact that radiation injury tends to be progressive also lends support to earlier surgical intervention.

*Surgery performed by Lieutenant Colonel Frank E. Hamilton, Walter Reed General Hospital.

However, some patients with ulcers demonstrable by x-ray and/or gastroscopy have shown a tendency to improve under medical care. It remains a matter of individual case judgment as to when surgery is required.

The operative therapy requires moderately radical partial gastrectomy. In this group of cases, a Hofmeister type of procedure was utilized. Any method could be employed except the Billroth I type, which requires end-to-end anastomosis of the incised end of the stomach to the duodenal stump. Because the duodenum is occasionally involved in the radiation effect, it is believed that healing may be delayed or faulty healing may induce a fatal outcome, if the end-to-end anastomosis is employed. The operation, therefore, is similar to that used for the radical treatment of ordinary peptic ulcer.

The differences and difficulties reside in the altered pathologic picture. It has been mentioned that the skin and abdominal wall are relatively free of the radiation changes. When the abdomen is opened, preferably by a transverse incision which allows better exposure, one can see the lesion which is characterized by an edematous, thickened whitish appearance and, when palpated, is definitely firmer than the normal stomach. The jejunum and duodenum are apt to show more of the white discoloration than the stomach. In Cases 1 and 4, a large penetrating ulcer with indurated edges could be felt. Both ulcers were in the prepyloric region and posteriorly. The vascularity was increased in all cases, particularly in the region of the first portion of the duodenum. Cases 2 and 3 demonstrated a generalized radiation effect without formation of large ulcers. It is conceivable that many small ulcers were present before medical treatment brought about healing.

The greatest difficulty in the operation is to establish whether or not the radiation effect can be completely eradicated at the duodenal end. The pathologic process gradually "melts away" into normal stomach or duodenum. The duodenal line of incision is limited because of the presence of the pancreatic and common bile ducts. The gastric line of incision could be more certainly established because the fundus of the stomach is out of the line of the x-ray portals and one is able to incise the stomach at a point known to be above the radiation change. In Case 2, the duodenum, although less involved than the stomach, was involved to such an extent that faulty healing was anticipated. One is not so much concerned with the presence of the process in the first part of the jejunum, because an anastomosis below the lesion in the jejunum can be accomplished. In Case 2, because of widespread jejunal injury, better judgment would have been to abandon the procedure and that would have been done except for the fact that the patient was obviously dying of uncontrollable hemorrhage. The risk of healing of the duodenal stump and anastomosis was felt to be his only chance for survival.

It was feared that the necessary manipulation for mobilization of the duodenum and the freeing of the curvatures might induce a hemorrhage which would be fatal in the chronic anemic state of the patients. In Case 1, the operator fortunately saw the gush of blood from the large branch of the middle colic vein which could be easily controlled by clamping under direct vision. None

of the other patients bled at the time of operation. The possibility of fatal hemorrhage into the gastrointestinal tract during the early steps of the operation is recognized.

The closure of the duodenal stump and the gastrojejunostomy offered no problem if these structures were normal. Healing obviously was unimpaired in all the cases except Case 2. The high intestinal fistula must have been present either in the duodenal stump which failed to heal properly or at some place in the long jejunal loop which was involved in the radiation effect.

SUMMARY

There have been presented six cases of radiation effect on the stomach requiring surgical intervention. Similar cases have not been previously reported elsewhere. Perforation of radiation-induced ulcers in the antral portion of the stomach was noted in three cases and hemorrhage was also noted in three cases, in one of which there was also a perforation. In the other case, an uncomplicated ulcer at the pylorus was found. Radical surgery was required in chronically ill patients in whom the procedure is made additionally difficult because of the presence of radiation injury to the small intestine in some cases. The result of the gastric surgery has been satisfactory but complications incident to radiation injury in other parts of the gastrointestinal tract have appeared in some cases. It is emphasized that patients receiving similar amounts of radiation without apparent gastrointestinal injury have been observed, accentuating the marked individual variability of response of the tissues of the gastrointestinal tract to radiation.

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A STUDY OF THE GASTRIC STOMA AFTER PARTIAL GASTRECTOMY

An Analysis of Ninety Gastric Resections

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IN FORMER years, we used to hear a great deal about the "stoma" that was made between the stomach and jejunum when a gastroenterostomy was done. Surgeons always made a point of demonstrating to their assistants and the admiring audience that the stoma, at the site of the anastomosis, was of good size and well placed. It was felt then, that if this was done, the operation would be a success. Surgeons went on making bigger and better stomas in the erroneous belief that patients with "peptic ulcers" would be cured. With the passage of time, however, it was soon found among thinking surgeons that regardless of the size or position of the stoma, these patients were not being cured. It was quite evident that the size or position of the stoma had nothing whatever to do with the success of the operation. It has been demonstrated rather conclusively that to be successful an operation for peptic ulcer must remove the maximum possible amount of gastric mucosa containing acid-forming glands, and the antral mucosa.[2]

It is generally felt among surgeons that the stoma is the entire diameter of the stomach that is used in the anastomosis.[3] Thus, in the Polya operation the stoma would be very large and in the Hoffmeister operation it would be much smaller.

In our series of ninety cases, the Polya type of anastomosis was the surgical procedure used except for seven cases in which a Hoffmeister modification was employed. This was found very useful in those cases in which the lesion was unusually high up on the lesser curvature and a safer anastomosis could be made by closing a part of the stomach stoma.

Eighty-one of the patients operated upon were men and only nine were women. Sixty-eight of the patients were operated upon for duodenal ulcers and twenty-one had gastric ulcers. One patient had a marginal ulceration. Our youngest patient was 22 years old, and the oldest was 72 years old.

After studying roentgenograms and sketches made from them, of these resections, we were led to the conclusion that the "true stoma" that resulted from partial gastrectomy was not the currently held wide diameter of the residual stomach, but was rather the narrow jejunal diameter into which the stomach empties (see Fig. 1). From an examination of Fig. 1, it is quite evident that the stomach can empty only as fast as the lumenal diameter of the jejunum

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TABLE I. PATIENTS OPERATED UPON

NAME	SEX	AGE	DIAGNOSIS	OPERATION	RESULTS
1. H. C.	M	22	Duodenal ulcer	Subtotal gastrectomy	Good
2. L. B. M.	F	27	Gastric ulcer	Subtotal gastrectomy	Good
3. J. K.	M	27	Duodenal ulcer	Subtotal gastrectomy	Good
4. J. K.	M	27	Gastric ulcer	Subtotal gastrectomy	Good
5. S. I. G.	M	30	Duodenal ulcer	Subtotal gastrectomy	Good
6. G. N.	M	32	Duodenal ulcer	Subtotal gastrectomy	Good
7. G. H.	M	32	Duodenal ulcer	Subtotal gastrectomy	Good
8. W. W. B.	M	32	Duodenal ulcer	Subtotal gastrectomy	Good
9. H. L.	M	31	Duodenal ulcer	Subtotal gastrectomy	Good
10. J. C.	M	34	Gastric ulcer	Subtotal gastrectomy	Good
11. C. H.	M	38	Duodenal ulcer	Subtotal gastrectomy	Good
12. A. L. T.	F	39	Duodenal ulcer	Subtotal gastrectomy	Good
13. W. F. G.	M	40	Duodenal ulcer	Subtotal gastrectomy	Good
14. C. M.	M	41	Duodenal ulcer	Subtotal gastrectomy	Good
15. T. S.	F	41	Gastric ulcer	Subtotal gastrectomy	Good
16. E. E.	M	41	Duodenal ulcer	Subtotal gastrectomy	Good
17. H. A.	M	41	Duodenal ulcer	Subtotal gastrectomy	Good
18. J. B.	M	42	Gastric ulcer	Subtotal gastrectomy	Good
19. R. T.	M	43	Duodenal ulcer	Subtotal gastrectomy	Good
20. M. B.	M	43	Duodenal ulcer	Subtotal gastrectomy	Good
21. C. M.	M	43	Duodenal ulcer	Subtotal gastrectomy	Good
22. H. G.	M	44	Gastric ulcer	Subtotal gastrectomy	Good
23. T. J.	M	44	Duodenal ulcer	Subtotal gastrectomy	Good
24. L. V.	M	45	Duodenal ulcer	Subtotal gastrectomy	Good
25. G. A.	M	45	Duodenal ulcer	Subtotal gastrectomy	Good
26. R. S. L.	M	44	Duodenal ulcer	Subtotal gastrectomy	Good
27. W. M.	M	46	Duodenal ulcer	Subtotal gastrectomy	Good
28. S. J. M	M	47	Duodenal ulcer	Subtotal gastrectomy	Good
29. A. W.	M	47	Gastric ulcer	Subtotal gastrectomy	Good
30. D. H.	M	47	Duodenal ulcer	Subtotal gastrectomy	Good
31. J. H. M.	M	47	Duodenal ulcer	Subtotal gastrectomy	Good
32. H. L.	M	47	Duodenal ulcer	Subtotal gastrectomy	Good
33. A. B.	M	48	Duodenal ulcer	Subtotal gastrectomy	Good
34. J. B. E.	M	48	Duodenal ulcer	Subtotal gastrectomy	Good
35. O. E. H.	M	49	Duodenal ulcer	Subtotal gastrectomy	Good
36. A. P.	M	47	Duodenal ulcer	Subtotal gastrectomy	Good
37. C. T. W.	M	48	Gastric ulcer	Subtotal gastrectomy	Good
38. F. B.	M	48	Duodenal ulcer	Subtotal gastrectomy	Good
39. C. B.	M	50	Duodenal ulcer	Subtotal gastrectomy	Good
40. M. F. F.	F	50	Gastric ulcer	Subtotal gastrectomy	Good
41. W. G.	M	50	Duodenal ulcer	Subtotal gastrectomy	Good
42. A. M.	F	50	Marginal ulcer	Subtotal gastrectomy	Good
43. K. H.	M	51	Duodenal ulcer	Subtotal gastrectomy	Good
44. E. D. S.	M	51	Duodenal ulcer	Subtotal gastrectomy	Good
45. E. M.	M	51	Duodenal ulcer	Subtotal gastrectomy	Good
46. L. B.	M	51	Duodenal ulcer	Subtotal gastrectomy	Good
47. J. M.	M	51	Gastric ulcer	Subtotal gastrectomy	Good
48. A. M.	M	52	Duodenal ulcer	Subtotal gastrectomy	Good
49. F. K.	M	52	Duodenal ulcer	Subtotal gastrectomy	Good
50. W. B.	M	52	Duodenal ulcer	Subtotal gastrectomy	Good
51. I. W.	M	53	Duodenal ulcer	Subtotal gastrectomy	Good
52. J. J.	M	53	Duodenal ulcer	Subtotal gastrectomy	Good
53. K. K.	M	54	Duodenal ulcer	Subtotal gastrectomy	Good
54. C. W. G.	M	54	Duodenal ulcer	Subtotal gastrectomy	Good
55. K. H.	M	54	Duodenal ulcer	Subtotal gastrectomy	Good
56. H. M.	M	55	Gastric ulcer	Subtotal gastrectomy	Good
57. F. G.	F	55	Duodenal ulcer	Subtotal gastrectomy	Good
58. W. P. M.	M	55	Duodenal ulcer	Subtotal gastrectomy	Good
59. G. M.	M	57	Duodenal ulcer	Subtotal gastrectomy	Good
60. H. B.	M	56	Gastric ulcer	Subtotal gastrectomy	Good
61. E. E.	M	56	Duodenal ulcer	Subtotal gastrectomy	Good
62. M. S.	M	56	Gastric ulcer	Subtotal gastrectomy	Good
63. J. H.	F	58	Gastric ulcer	Subtotal gastrectomy	Good
64. R. H.	M	58	Gastric ulcer	Subtotal gastrectomy	Good

TABLE I. (CONT'D)

NAME	SEX	AGE	DIAGNOSIS	OPERATION	RESULTS
65. A. W.	M	59	Duodenal ulcer	Subtotal gastrectomy	Good
66. T. P.	M	59	Gastric ulcer	Subtotal gastrectomy	Good
67. J. H. C.	M	59	Duodenal ulcer	Subtotal gastrectomy	Good
68. A. B.	M	57	Duodenal ulcer	Subtotal gastrectomy	Good
69. C. E.	M	57	Gastric ulcer	Subtotal gastrectomy	Good
70. J. L.	M	57	Duodenal ulcer	Subtotal gastrectomy	Good
71. M. C.	M	34	Duodenal ulcer	Subtotal gastrectomy	Good
72. J. W.	M	51	Duodenal ulcer	Subtotal gastrectomy	Good
73. L. P.	F	36	Duodenal ulcer	Subtotal gastrectomy	Good
74. H. W.	M	51	Duodenal ulcer	Subtotal gastrectomy	Good
75. W. H.	M	60	Duodenal ulcer	Subtotal gastrectomy	Good
76. M. D.	M	60	Duodenal ulcer	Subtotal gastrectomy	Good
77. T. H. H.	M	61	Gastric ulcer	Subtotal gastrectomy	Good
78. J. D.	M	61	Duodenal ulcer	Subtotal gastrectomy	Good
79. G. A. H.	M	62	Gastric ulcer	Subtotal gastrectomy	Good
80. H. F.	M	62	Duodenal ulcer	Subtotal gastrectomy	Good
81. J. C. C.	M	62	Gastric ulcer	Subtotal gastrectomy	Good
82. J. K.	M	64	Duodenal ulcer	Subtotal gastrectomy	Good
83. G. M.	M	66	Duodenal ulcer	Subtotal gastrectomy	Good
84. J. G.	F	66	Duodenal ulcer	Subtotal gastrectomy	Good
85. D. W.O.	M	71	Duodenal ulcer	Subtotal gastrectomy	Good
86. E. G. B.	M	77	Gastric ulcer	Subtotal gastrectomy	Good
87. G. P.	M	72	Duodenal ulcer	Subtotal gastrectomy	Good
88. H. W.	M	47	Duodenal ulcer	Subtotal gastrectomy	Good
89. A. K.	M	56	Duodenal ulcer	Subtotal gastrectomy	Good
90. R. C.	M	53	Duodenal ulcer	Subtotal gastrectomy	Good

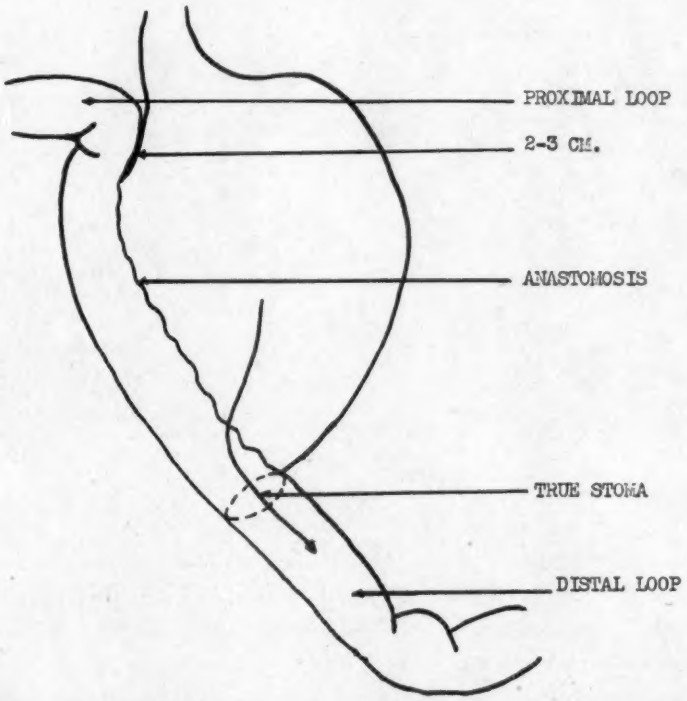

Fig. 1.—Note that a Polya type of resection has been done. The proximal loop has been sutured along the lesser curvature for two to three centimeters. Note the true gastric stoma as being the lower end of the anastomosis and consisting of the circumference of the jejunum into which the stomach empties.

to which it is attached can accommodate its contents. Since the proximal loop of jejunum is nonfunctional (see Figs. 2 and 3), that portion of the jejunum along the entire length of the anastomosis becomes actually merely a part of the stomach wall (see Fig. 2). It we disregard the proximal loop, which we must since it is nonfunctional, it would be quite evident that only the lower end of the anastomosis becomes part of the true gastric stoma. As an analogy, if one considers the remaining stomach, with the jejunum as being its lower wall as a funnel, which in truth it is, then the stoma must of necessity be that narrowed portion which carries the gastric contents into the jejunum. A glance at Fig. 1 readily shows that this must be only at one point and not along the entire length of the anastomosis. This point becomes more obvious if one will note that in Fig. 5, which was taken four years following gastrectomy, the lower gastric wall (jejunum) has bulged considerably downward almost restoring the original size of the stomach, but the "true gastric stoma" which is now displaced to the left still remains the same caliber. Fig. 3 represents the stomach and jejunum including the anastomosis removed from a patient at autopsy.

A. *B.*

Fig. 2.—*A*, Note the down-pouching of the jejunal wall of the anastomosis. *B*, This patient was operated upon four years previously. Note how the true gastric stoma has been displaced along the greater curvature to the left. This is not a true displacement, but is due to the down-pouching of jejunum. Note also that the barium stream narrows and then widens, suggesting peristaltic activity at the true gastric stoma.

This patient had been operated upon four days previously (not by us) and had suddenly died of coronary occlusion. We removed the stomach in toto and injected barium through the esophagus. The stomach was then held up by the esophagus and the barium permitted to run downward. Roentgenograms were then taken (Fig. 3). Note that here, too, there is no barium in the proximal loop, and that the main stream of barium runs downward through the true

gastric stoma. It is quite evident that the stream of barium, when seen under fluoroscopy, runs along the lesser curvature striking the jejunal wall and then rebounding to the greater curvature and passing through the true gastric stoma. Since this is then the true gastric stoma, great care must be taken in performing the anastomosis to prevent rotation of the jejunum onto the greater curvature of the stomach which so commonly produces obstruction at the lower end of the anastomosis and so obstructs the true gastric stomo with disastrous consequences.

A study of roentgenograms (Figs. 2 and 4), taken several years post-operatively shows rather well that the barium passes through this stoma as it would through the pylorus.

Fig. 3.

Fig. 4.

Fig. 3.—Autopsy specimen. Note that there is no barium in the proximal loop. Note that the barium stream passes through the lower end of the anastomosis, that is, true gastric stoma.

Fig. 4.—Note the out-pouching of the jejunal wall producing a relative displacement of the true gastric stoma to the left. Note the constriction of the barium stream at the true gastric stoma suggesting sphincteric action at this point.

During the first week postoperatively, due to stomal edema there are always varying amounts of gastric retention dependent upon the degree of edema at the true gastric stoma. The retained fluids are siphoned off by the use of a Levin tube. If the entire circumference of the anastomosis were the true outlet, it would take a tremendous amount of edema to produce a delay in gastric emptying much less a retention. Because the true gastric stoma is that small funnel-like opening at the lower end of the anastomosis, a slight amount of edema at this point readily impedes gastric emptying. Even after all

edema has subsided, such patients must be warned not to eat too much or too fast because the narrowed gastric outlet is not large enough to permit the passage of solid foods through it very rapidly. On the other hand, liquid foods might pass through the stoma faster than the loop of jejunum into which it empties can accommodate it. Again, the patient would suffer from epigastric distress.

With the passage of time and the gradual enlargement of the residual stomach and its jejunal wall by stretching, it becomes possible for such patients to eat larger meals without discomfort. If it were true that the entire width of the remaining portion of the stomach were the stoma, this could not occur because emptying would occur too rapidly for the stomach ever to become distended and so stretched. Clinical observations of patients subjected to

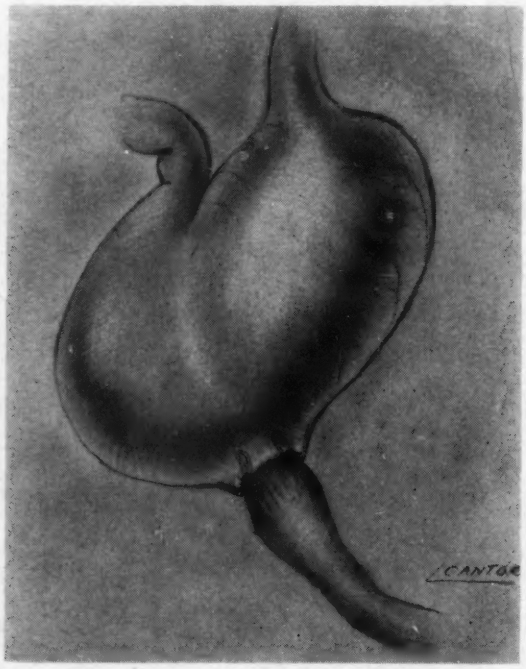

Fig. 5.—Drawing of anatomy found four years following Polya Operation. Note the outpouching of the jejunal wall which has become in reality the lower gastric wall. The true gastric stoma is displaced to the left. There was definite sphincteric action noted at the point of constriction at the true gastric stoma. There was a down-pouching of the stomach and jejunum at the true gastric stoma as noted in this drawing.

partial gastrectomy show that these stomachs do distend,[4, 5] and roentgen studies show very well that the true outlet of the stomach is in fact the diameter of the distal loop of jejunum and not the entire circumference of the stomach (see Figs. 2 and 4). That portion of jejunum opposite the cut end of the stomach is then in actuality part of the stomach wall.

SUMMARY

A study of ninety patients who were subjected to partial gastrectomy for duodenal or gastric ulcers has led us to to one obvious conclusion, that is: that the true gastric stoma is not the entire width of the remaining portion of the

stomach, but must of necessity be that narrowed outlet which leads into the jejunum. This outlet cannot be larger than the lumenal diameter of the jejunum. Since this is so, great care must be exercised to avoid rotation of the jejunum onto the greater curvature of the stomach which would obstruct the true stoma. Regardless of the type of anastomosis performed, the size of the true gastric stoma remains the same. Roentgen studies show rather conclusively that with the passage of time the residual stomach and its jejunal lower wall dilates so that more food can be accommodated and the true stoma then behaves much like the pylorus. Ultimately a balance is reached so that these patients are able to eat a normal amount of food without discomfort.

CONCLUSIONS

1. The true gastric stoma is not the entire circumference of the residual stomach.

2. The true gastric stoma is only that narrowed jejunal diameter into which the stomach empties, and is found at the lower end of the anastomosis.

3. The size of the true gastric stoma remains the same regardless of the type of gastric resection performed.

4. With the passage of time, the jejunal wall of the stomach pouches outward and the residual stomach dilates so that the true gastric stoma becomes displaced to the left.

5. Roentgenograms taken four years postoperatively show that the true gastric stoma now behaves much like the pylorus with regard to peristaltic activity.

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CHOLECYSTECTOMY AND PARTIAL HEPATECTOMY FOR CARCINOMA OF THE GALL BLADDER WITH LOCAL LIVER EXTENSION

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RECENT advances in anesthesia, supportive intravenous therapy, and the easy availability of blood transfusion have greatly extended the scope for curative and palliative surgical procedures. Many operations previously considered impractical or too hazardous may now be undertaken not lightly, but certainly with the thought that a reasonable degree of success is to be anticipated.

This case is presented as another instance of partial hepatectomy and cholecystectomy for carcinoma of the gall bladder with metastasis grossly localized to the adjacent liver.

CASE REPORT

J. M., aged 61 years, a barber, was admitted to the medical service of the Coney Island Hospital on Sept. 27, 1945. For fifteen months he had had recurring attacks of right upper abdominal colicky pain. He tolerated fatty foods poorly. These induced flatulence and a feeling of abdominal distention. There was a loss of sixty to seventy pounds in the year preceding hospital admission. Gall bladder studies indicated a nonfunctioning gall bladder.

Physical examination revealed a fairly well-nourished man not acutely distressed, who showed evidence of recent weight loss. Examination was essentially negative except for the local findings. On abdominal palpation a tender mass could be felt in the right upper abdomen. The liver edge was palpable two fingerbreadths below the costal margin and was sharp except where it merged with the mass which was interpreted as being gall bladder. There was moderate abdominal spasm. In the twelve-day period of observation prior to operation, a febrile course persisted. The temperature ranged from 100 to 102° F. Gall bladder x-ray series on Oct. 5, 1945, again revealed a nonfunctioning gall bladder. One large ring-shaped shadow could be seen in the right upper quadrant. This had the appearance of a gallstone.

Laboratory data were as follows: hemoglobin, 83 per cent; white blood cells, 9,800; Wassermann was negative, urine negative, blood sugar 101 mg. per 100 c.c., and urea 12 mg. per 100 c.c. The total blood protein was 6.5 Gm., albumin 3.9, globulin 2.6, cholesterol 194 mg. per 100 c.c., cholesterol esters 71 mg. per 100 c.c., and icterus index 5.

On Oct. 8, 1945, a laporotomy was performed under spinal anesthesia, through a right upper rectus muscle-splitting incision. The gall bladder was enlarged. The fundus was hard and had a peculiar whiteness to it. The entire distal two-thirds of the gall bladder was intimately fused with the overlying liver bed. The liver around the gall bladder bed contained numerous various-sized nodules—obviously metastatic carcinomatous nodules. The involved area in the liver was localized to the region about the gall bladder. No other gross metastases could be seen. The glands in the porta hepatis were not enlarged. The gall bladder also contained numerous calculi. The proximal third, the neck, and cystic ducts were free of neoplastic disease. The condition was apparently one of carcinoma of the fundus of the gall bladder with localized metastases to the surrounding liver. The cystic duct was isolated, clamped, cut, and ligated. The cystic vessels were ligated and cut. A series of deep mattress sutures was placed through the liver surrounding the grossly involved portion and tied. The

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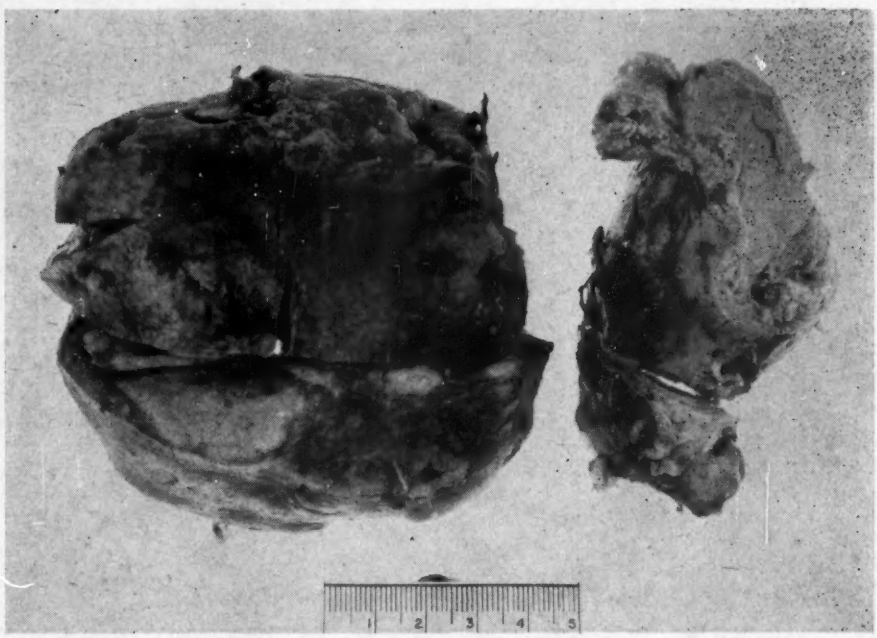

Fig. 1.—Gall bladder and segment of excised liver, anterior aspect.

Fig. 2.—Gall bladder and segment of excised liver, posterior aspect.

involved liver lobe and attached gall bladder was then resected. Hemostasis was relatively easy to obtain. An occasional bleeding area was seen. This could be clamped and ligated readily. The surrounding deep sutures were effective and controlled most of the potential bleeding. After the segment of liver was removed, the liver gap was closed by approximating the cut surfaces by several deep sutures. A Penrose drain was placed down to the foramen of Winslow and the abdomen closed in layers. Postoperative recovery was uneventful except for some complicating bilateral pulmonary atelectasis which cleared spontaneously. The patient was discharged on Oct. 29, 1945 (twenty-fourth day postoperative), the wound well healed, and symptom free.

Figs. 1 and 2 show the gall bladder and the segment of liver involved. Fig. 3 is a microphotograph of the lesion, an epidermoid carcinoma of the gall bladder.

When seen several months after operation, the patient was relatively well. He then moved to another community, where he died approximately seven months postoperatively, presumably from recurrence, although the cause of death could not be ascertained.

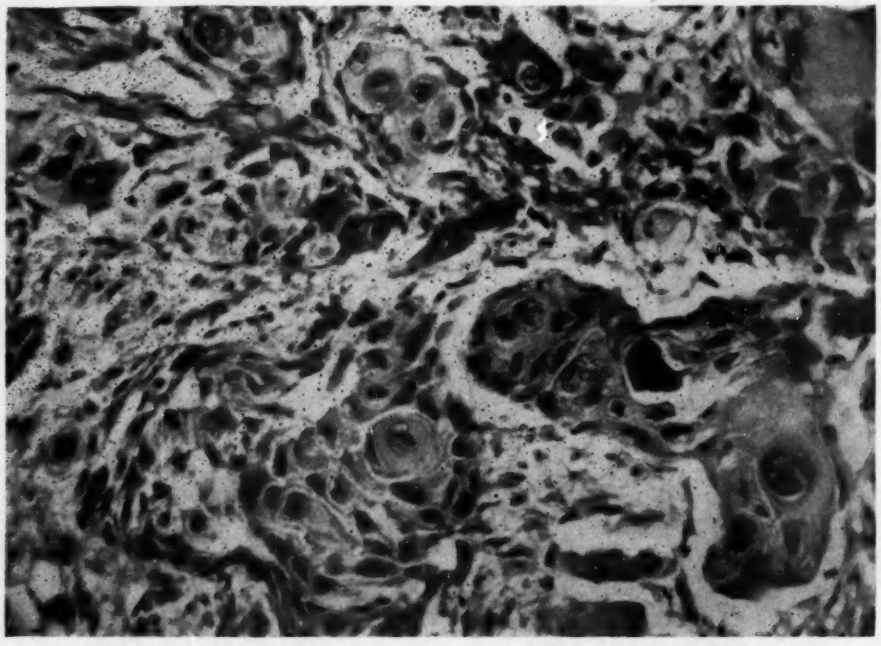

Fig. 3.—Microphotograph, epidermoid carcinoma of gall bladder (high power).

DISCUSSION

In 1891 Keen[1] excised an adenoma of bile ducts by Paquelin cautery and fingernail enucleation, in 1897 he removed a liver angioma by extraperitoneal elastic constriction, and in 1899 he excised the left lobe of the liver involved by carcinoma by Paquelin cautery. Hemorrhage was controlled by the cautery, digital compression, and suture ligature. All three patients recovered from the operation. Seventy-three other cases of partial hepatectomy for various causes were collected from the literature.

Thompson[2] successfully resected a gumma involving contiguous parts of the right and left liver lobes. He collected cases of liver resection and reported six deaths in forty-two cases.

TABLE I. CASES OF CARCINOMA OF GALL BLADDER WITH LIVER EXTENSION SUBJECTED TO HEPATECTOMY AND CHOLECYSTECTOMY

CASE NO.	AUTHOR AND YEAR	NO. OF CASES	PROCEDURE	RESULTS IMMEDIATE AND ULTIMATE	REMARKS
1	Quoted by Keen,[1] Kuester, 1892	1	Tumor exteriorized, elastic ligatures	Died from septicemia	Operative mortality
2	Watson, 1896	1	Rubber ligatures through normal liver tissue about the lesion, allowed to slough out	Recurrence in 2 mo. and death	Delayed operative mortality
3	Ulman, 1897	1	Excision of tumor, of gall bladder, and resection of ductus hepaticus, liver stump extraperitonealized	Recurrence and death 6 mo. later	Early recurrence
4	Winiwater, 1897	1	Hemostatic silk sutures through liver substance, thermocautery excision of gall bladder, and infiltrated portion of liver; iodoform gauze packing	Death in 6 weeks	Delayed operative mortality
5	Robson,[15] 1898	3	(1) Exteriorized gall bladder and involved liver-elastic ligatures about knitting needles	Died of recurrence 8 mo. later; early recurrence	These were 3 cases out of 35 cases of malignant disease of the liver and bile passages where surgery appeared feasible
6			(2) Exteriorized gall bladder and liver—elastic ligatures	Died of recurrence 6 mo. later; early recurrence	
7			(3) Case with numerous adhesions treated as first cases	Died of shock several hours postoperatively; operation mortality	
8	Quotes Hochnegg (Vienna)	1	Removal of gall bladder and adjoining liver for carcinoma	3 yr. survival; well 2 yr.	No liver enlargement at death; died of cachexia at 3 yr.
9	Monks,[16] 1899	1	Excised gall bladder, liver segment, and part of anterior wall of stomach	Patient well 9 weeks later, no further observation	No follow-up
10	Terrier and Auvray,[17] 1900 Quotes (1) Czerney, 1893	1	Cholecystectomy and liver resection (iodoform gauze packing of cut liver section)	Operative recovery, died 2 mo. postoperatively, details not known	
11	(2) Czerney, 1898	1	Cholecystectomy, excision of metastatic nodule from liver parenchyma	Recurrence 7 mo. postoperatively liver metastases; died 10 mo postoperative	Regional lymph nodes involved at original operation
12	(3) Duret, 1898	1	Resection of liver and gall bladder for extensive growth of gall bladder infiltrating the liver	Operative recovery; no follow-up	
13	(4) David Grieg, 1897	1	Resection of liver and gall bladder	Operative recovery—no follow-up	

(Continued on following pages.)

TABLE I. (CONT'D)

CASE NO.	AUTHOR AND YEAR	NO. OF CASES	PROCEDURE	RESULTS IMMEDIATE AND ULTIMATE	REMARKS
14	(5) Heidenhain, 1896	1	Resection of liver and gall bladder	Recurrence 3 mo. postoperatively	
15	(6) Hollander, 1896	1	Resection of liver and gall bladder	In good health 1½ yr., possibly 2—no follow-up after that	
16 17	(7 & 8) Krouse, 1898	2	Resection of liver and gall bladder	No other information as to follow-up, operative recovery but no follow-up	
18	(9) Terrier, 1895	1	Resection of liver and gall bladder (very extensive lesion)	Operative recovery; died six months later; cachexia	
19	Mayo,[18] 1902	1	Cholecystectomy and liver resection; resected common duct, and portion of doudenum in addition	Early recurrence	
20	Garre,[3] 1905	1	Cholecystectomy and wedge-shaped resection of liver; isolated metastasis, excised separately	Recurrence (time not stated)	
21	Frankau,[19] 1913	1	Resected gall bladder with wedge of liver; interposed omentum and sutured the liver	Recovery patient alive and well 15 mo. postoperatively	
22 23 24	Walton,[20] 1922	3	In each a relatively large portion of liver was removed with gall bladder	All 3 cases had recurrences in peritoneum or liver within a few months; longest period of freedom was 6 mo.	Operation is easy and hemorrhage is readily controlled
25 26 27	Finsterer,[21] 1932	1 1 1	Cholecystectomy and resection Cholecystectomy and resection Resection of liver and gall bladder	Early recurrence Sudden death 6 mo. later Well 6½ yr. later	
28	Gray,[22] 1934	1	Gall bladder and attached portion of liver—about 2 cm. of normal tissue all around excised; hemostasis by electrocoagulation and through mattress sutures	Immediate recovery; no follow-up	Prognosis guarded in this case .9% incidence of carcinoma of gall bladder in 22,365 operations on gall bladder or biliary tract

29	Hochberg and Kogut,[23] 1939	1	Gall bladder and attached portion of liver—about 2 cm. of normal tissue all around excised; hemostasis by electrocoagulation and through mattress sutures	Patient well 14 mo. later and gained 26½ pounds	
30	J. R. Paine[24] (personal comunication to Mattson), 1942	1	Excision of portion of liver with gall bladder to eliminate contiguous metastasis	Successful resection; follow-up not given	
31	Boladeres,[25] 1943	1 Personal	Cholecystectomy and partial hepatectomy, at second operation (2 mo. later); further removal of liver for incomplete excision of malignancy	One year later patient was well and had gained 20 pounds	
	Collected from the Literature				
32	Chiaserini	1	Cholecystectomy and partial hepatectomy	Died 1 mo. later	
33	Polizzi	1	Cholecystectomy and partial hepatectomy	Patient well 1 yr. later	
34	Gioja	1	Cholecystectomy and partial hepatectomy	Patient died 1 yr. later.	
35	Lambret	1	Cholecystectomy and partial hepatectomy	Patient well 5 mo. later, no further follow-up	
36	Sheinfeld, 1945	1	Excision of portion of liver with gall bladder to eliminate contiguous metastases	Well 3 mo. postoperatively, died 4 mo. later, cause unknown but presumably due to metastasis	

TABLE II. CARCINOMA OF THE GALL BLADDER—CHOLECYSTOMY OR OTHER OPERATIONS

AUTHOR	DATE	NO. OF CASES	NO. OF PATIENTS OPERATED UPON AND FOLLOWED	NO. OF CHOLECYSTECTOMIES	REMARKS (THE MORE FAVORABLE CASES AFTER CHOLECYSTECTOMY)
E. Quénu[26]	1908	(93 collected cases, 17 where liver resection was done) 76	39 (Cases where liver resection was done are excluded)	39	5 cases as follows: No recurrence at 4½ yr., 3 yr., 26 mo., 2 yr., 1 yr. 1 died at 2½ yr.
Smithies[27]	1919	23	23—(11 explorations, 7 cholecystostomies, 1 gastroenterostomy)	4	2 alive at end of 4 yr.
Finsterer[21]	1932	2	1	1	1 early death
Quotes					
Koerte		1	1	1	Alive 5 yr. later
Worner		1	1	1	3 patients well after 3 yr.
Kummel		1	1	1	
Ringel		1	1	1	
Shelly & Ross[28]	1932	19	19	13	1 patient living 6½ yr. (14 died within 3 weeks)
Aiga[29]	1935	1	1 (also resected involved common duct)	1	Alive and well 7¾ yr. postoperatively
Boyce & McFetridge[30]	1936	25	19 (14 explorations, 1 cholecystostomy)	4	1 case with possible hope of survival—malignancy an incidental finding
Rhodes & Greenblatt[31]	1937	24	22	5	1 patient alive and well after 5 yr.

Cooper[32]	1937	48	45 (21 cases with exploration and biopsy)	16	1 alive and well 2 yr.; 25% mortality in cholecystectomy cases; 38% mortality in exploration; average duration of life 3½ mo. 5 cholecystectomies appeared to have no metastasis but 4 patients died in 10 mo. from recurrence after cholecystectomy
Lam[33]	1940	34 autopsy 1	33 (Explorations and biopsy 23, cholecystostomy 1)	9 (3 had radium in addition)	1 alive and well after 5 yr.; lesion not suspected at operation.
Quénu & Masseboeuf[34]	1941	1	1	1	Survived 14 yr. Died of intercurrent ailment
Greenlee, Hamilton, & Ferrar[35]	1941	5	5	3	1 died at 13 mo. (others died sooner)
Mattson[36]	1942	60	No details		No successful case
Vadheim, Gray, & Dockerty[37]	1944	77	54	54	7 alive and well 5 yr. (4 more than 13 yr.), grade 1 1 survival 6 yr., (grade 2) 1 died at 18 mo., (grade 4) 3 died of other causes, 2 surviving 5 yr., (grade 1)
Finney & Johnson[38]	1945	18	18	3	1 died at 16½ mo., 1 at 25 mo.

Garré[3] in 1907 published six cases of liver resections for carcinoma, sarcoma, and echinococcus disease.

In the *Proceedings of The Royal Society of Medicine,*[4] 1922-1923, a symposium on partial hepatectomy was presented.

Grey Turner[5] presented a case of an adenoma, a large lobulated tumor in the right lobe of the liver weighing two pounds and three ounces, which he successfully resected. He quoted a case of Dr. George Hume. This was a liver resection for a large and localized liver recurrence of a stomach carcinoma. Death occurred twelve months later from further recurrence.

Philip Turner[6] removed a bleeding adenoma by Paquelin cautery but the patient succumbed to shock in the immediate post-operative period.

A large primary carcinoma in the right lobe of the liver was excised together with the gall bladder by Wright.[7] He stated that cutting boldly through the liver is safe. Hemorrhage can be controlled by hot packs and then picking up bleeding vessels. Other types of liver tumors and resections were presented.

Abel[8] removed the entire left lobe for adenocarcinoma of bile duct origin. The specimen weighed five pounds. However, there was recurrence nine months later.

The liver has been resected successfully in cases of direct invasion by carcinoma from a contiguous primary carcinoma as in carcinoma of the stomach, colon, or kidney.

Cattell[9] resected a large solitary metastasis of the liver at the first stage of a two-stage abdominoperineal resection for carcinoma of the rectum. The patient was well one year later.

Pickrell and Clay[10] removed the left lobe three times in a four-month period for carcinoma, hemangioma, and gumma.

Packard and Stevenson[11] reported the excision of a large hepatoma from the right lobe of a boy of 13 months.

Numerous instances of liver resection are present in the literature. Most of these were successfully performed. By correspondence, Tinker and Tinker[12] in 1939 collected fifty-nine instances of liver resections by members of the American Surgical Association. Most of these were presumably unpublished. This operation must undoubtedly have been performed many more times without publication. Very likely the unsuccessful cases were not reported. However, there is an abundant literature now extant, which illustrates that the majority of liver lesions suitable for excision may be excised whether in the right or left lobes, even if not pedunculated, without a prohibitive mortality or morbidity rate.

Regarding the specific problem presented by this case report, the question of whether the procedure is worth while arises. Table I is a summary of 36 cases collected, where the gall bladder and contiguous liver were excised for carcinoma and direct extension into the liver or localized liver metastasis. Immediate operative mortality was 5.5 per cent (2 cases), delayed operative mortality 8.3 per cent (3 cases), a total operative mortality of 13.8 per cent. Early recurrences occurred in 38.8 per cent (14 cases), 22.2 per cent (8 cases)

recurring within six months and 16.6 per cent (6 cases) between six months to a year. Good palliative, or possible good long time results are noted in 19.4 per cent (7 cases). One patient died three years postoperatively of metastases, two patients were well one year postoperatively, three were well at 14, 15, and 18 months, respectively, and one 6½ years after operation. Twenty-two per cent or eight patients made operative recoveries but had no adequate follow-up studies. One patient died one month and another six months postoperatively from possible unrelated causes. It must be remembered that these cases are collected from the literature and may form a selected group favoring the cases with relatively better results since those in which poor results were obtained may have remained unpublished. Nevertheless, this group of cases merits consideration. The results compared with those cases were simple cholecystectomy, exploration with or without biopsy, or other less radical procedures upon the gall bladder and liver were done, are favorable.

Table II is a collection of reports of various series of gall bladder carcinoma and some single or small series case reports. Four hundred seventeen cases are collected. Two hundred eighty-four patients were operated upon. Cholecystectomy was performed 157 times. In twenty-eight cases there are possible good long-time results, 9.8 per cent of the total number of patients operated upon or 6.7 per cent of the total number of cases collected. There are 16 five-year, 3 four-year, 4 three-year, 3 two-year, and 1 one-year survivals, alive and well at that time. The survival time is not mentioned of the other case placed in this category. Five patients (1.7 per cent of the patients operated upon) lived 30, 25, 18, 16½, and 13 months, respectively, following operation. The remainder all succumbed within a relatively short time. Immediate operative mortality cannot be given from the data available. In Cooper's series it was 25 per cent. Walters and Snell[13] give it as 10 per cent. In evaluating the factors influencing survival time or recovery, Webber's[14] work must be considered. In a study of thirty patients who had been subjected to cholecystectomy from the point of view of grade of malignancy, Broders' classification, he noted the following: Local extension and metastasis were considerably higher in grade 3, or higher, carcinoma. The postoperative length of life was considerably better in the lower grade lesions.

From a survey of these cases collected, liver resection where possible appears to be of definite palliative value. The results in general are, however, poor when compared with the results of radical surgery for carcinoma of other organs.

SUMMARY

A case of epidermoid carcinoma of the gall bladder with metastases localized to a resectible area of the liver is presented.

The feasibility and palliative value of liver resection for carcinoma of the gall bladder and local liver extension are discussed.

For comparison, the results obtained with cholecystectomy for early carcinoma, or simple exploration and biopsy for more advanced carcinoma, are given.

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THE CAROTID SINUS SYNDROME: ITS SURGICAL TREATMENT

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IN RECENT years many excellent contributions have appeared in the literature on the anatomy[2, 9, 17, 20] and physiology[1, 3, 4, 7, 9, 10, 22, 23] of the carotid sinus. In 1933, Weiss and Baker called attention to the significance of the carotid sinus reflex, particularly in its abnormal phases, in man.[22] They presented evidence that an abnormally sensitive carotid sinus reflex could be responsible for the syndrome of spontaneous attacks of vertigo, syncope, and convulsion or milder manifestations. A number of observers have confirmed the existence of what has come to be known as the carotid sinus syndrome.[5, 11-13, 18, 23] Many individuals with an abnormality of the carotid sinus reflex suffer only mild symptoms; however, there are a number of the more severely afflicted persons in whom the symptoms of dizziness, vertigo, and syncope may not only be dangerous but totally disabling. These patients have been afforded relief by surgical denervation of the carotid sinus. We wish to report three cases of carotid sinus syncope, and to review briefly the significant aspects of the carotid sinus syndrome.

The carotid sinus syndrome of spontaneous attacks of dizziness and fainting occurs as a result of a hypersensitive state of the carotid sinus reflex. It results through one or more of three main reflex arcs. The afferent or sensory limb is probably always the same, but the motor pathways differ.

The carotid sinus is a small bulbous dilatation of the first part of the internal carotid artery. Its walls are supplied by a dense plexus of nerves and sensitive end organs, some of which appear to respond to stretch or pressure and others to chemical stimuli. Impulses which result from such stimuli arise in the carotid sinus and travel centrally to the medulla.[9] The principal afferent pathway is by the carotid sinus nerve (nerve of Hering), which connects with the glossopharyngeal nerve, the vagus nerve, the cervical sympathetic chain, and occasionally the hypoglossal nerve.[9, 17, 20] The three motor pathways responsible for syncope involve the vagus nerve, the vasomotor-depressor nerves, or the central motor pathways, the clinical picture being determined by the efferent or motor pathways of the reflex.[7]

The first or vagal type carotid sinus reflex is characterized by bradycardia, asystole, cardiac arrhythmia, hypotension, and finally cerebral anoxemia which may lead to convulsions or unconsciousness. The second or depressor type is characterized mainly by vasodilatation and a fall in blood pressure. Cardiac arrhythmia is not present but there may be cerebral anoxemia with resulting unconsciousness or convulsions. This is the least common and usually accompanies one of the other two types. The third or cerebral type is characterized by sudden unconsciousness with no change in pulse rate or blood pressure and

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without intervening symptoms. Commonly, a mixed type is present, the type of syncope being classified according to the dominant motor pathway involved.[7] The vagal type of sinal syncope can be prevented by the administration of atropine which paralyzes the vagal endings, or by epinephrine through its local stimulating effect on the ventricles. The depressor type of reaction is abolished by epinephrine through its constricting action on the small blood vessels. Anesthesia of the carotid sinus induced by procaine hydrochloride or surgical denervation of the carotid sinus will abolish an abnormal response of any of the three types.

In a normal person the mechanical stimulation of the carotid sinus does not produce symptoms. In a patient in whom the carotid sinus is abnormally sensitive, mechanical or chemical stimulation results in many symptoms as well as a specific effect on the blood pressure. Such patients complain of sudden attacks of dizziness and unconsciousness with or, more rarely, without convulsions.[22] These attacks may occur without warning but are usually preceded by a definite aura which consists of weakness, dizziness, blurring of vision, and epigastric distress, the patient feeling as though he were going to faint. Such syncopal attacks are usually associated with hyperpnea, pallor, perspiration often profuse, falling, convulsive movements, declining blood pressure, slowing of the cardiac rate, and cardiac arrhythmia. Unconsciousness may last a few seconds to a few minutes; recovery, however, is usually prompt. The frequency and severity of the attacks vary greatly, even in the same person. The precipitating factors cannot always be discovered but often attacks result from turning the head suddenly, stooping, looking up, pressure on the sinus in resting the head on one hand, wearing a tight collar, or changing the position of the body quickly. Fatigue, emotional upsets, and menstruation may precipitate the symptoms. In many cases, however, no cause can be found. Symptoms almost always occur when the patient is in the upright position. Carotid sinus syncope is more common in middle-aged and elderly persons; however, it occurs rarely in young people. Not infrequently, it is associated with such disorders as arteriosclerosis, hypertension, emotional instability, syphilis, cervical lymph adenopathy, and digitalis intoxication.[23]

The diagnosis[23] of hyperactive carotid sinus is made from the history and by inducing an attack of syncope by making digital pressure over the carotid sinus with the patient in the upright position. Both sinuses should not be stimulated simultaneously. Infiltration of the region of the sinus with 1 per cent procaine will abolish an induced attack, and also prevent the reproduction of an attack by mechanical stimulation, thus serving to distinguish true attacks from hysteroneurosis. At the time of manipulation, changes in the pulse rate, blood pressure, and, if possible, the electrocardiogram should be recorded. One side is always more sensitive than the other. It is important that, as far as possible, the patient be classified as to type: vagal, pressor, or cerebral. Carotid sinus syncope may simulate atypical petit mal, grand mal, Ménière's disease, hysteria, narcoleptic or cataleptic seizures; however, these attacks cannot be induced by stimulation of the carotid sinus.

CASE REPORTS

CASE 1.—A housewife, aged 59 years, was seen in the Clinic in February, 1933, complaining of recurrent attacks of syncope for fifteen years. At first the attacks were infrequent and were characterized by "feeling weak," "a sensation of everything turning dark," and loss of consciousness. They were of two to ten minutes' duration and occurred only when she was in the upright position. There was no biting of the tongue, incontinence, or convulsions. They were not precipitated by any specific movement; however, they occurred more frequently during menstruation and at the time of the menopause. During the previous year the syncopal attacks had occurred with increasing frequency and severity and without warning. Two weeks prior to examination she had fallen in the bathroom during an attack and lacerated her scalp badly.

Physical examination revealed moderately generalized arteriosclerosis. The heart was not enlarged. Blood pressure was 142 mm. systolic and 74 mm. diastolic; the pulse rate 70. Laboratory studies of the blood and urine, including a blood sugar and serum calcium, were within normal limits. The electrocardiogram was essentially normal.

Pressure over the right carotid sinus caused no essential change in the blood pressure, cardiac rate, or state of consciousness. Pressure over the left carotid sinus caused a marked drop in blood pressure, slowing of the pulse rate, and syncope. Denervation of the left carotid sinus was done March 10, 1933. She was discharged improved on March 15, 1933.

The patient was last seen May 15, 1937, four years and two months following operation. There had been no fainting since operation. She complained of an occasional attack of pain in the face, beginning in the nose and spreading over the head. Except for slight ptosis of the left eye and slight swelling about the scar, examination gave negative results. Blood pressure was 155 mm. systolic and 85 mm. diastolic. No changes could be induced by pressure on the carotid sinus.

CASE 2.—A housewife, aged 61 years, was seen in the Clinic in June, 1939, complaining of rectal bleeding and constipation of one year's duration. Examination revealed carcinoma of the rectum. On June 15, 1939, an abdominoperineal resection was done. Convalescence was uneventful. She gained weight and strength and managed the colostomy well.

The patient returned to the Clinic in January, 1942, complaining of dizziness and syncope. For many years she had had attacks of dizziness but not until the past three years had they been associated with falling and syncope. She had suddenly become dizzy, lost consciousness, and had fallen several times during the past year. Within the last two months she had fallen during an attack and fractured the clavicle. She was aware that turning the head to the left or raising the left arm had something to do with precipitating the attacks of dizziness. She had been unable to prevent them by medical measures. She had no complaints suggestive of recurrent malignant disease.

Examination revealed the patient to be well developed, with a functioning colostomy. A moderate degree of arteriosclerosis was present. The heart was not enlarged. A small supraclavicular lipoma was present on the right side of the neck. Blood pressure was 150 mm. systolic and 85 mm. diastolic; the cardiac rate was 80. Laboratory studies of the blood and urine gave negative results. The electrocardiogram was essentially normal.

Pressure over the right carotid sinus caused no change in the blood pressure or cardiac rate. Pressure over the left carotid sinus caused marked slowing of the pulse, asystole for four seconds, a fall in blood pressure, vertigo, and syncope. Excision of the right supraclavicular lipoma and denervation of the left carotid sinus was carried out on Feb. 1, 1942.

During a four year follow-up there has been no return of the spontaneous attacks of dizziness and syncope. Carcinoma of the ala of the nose developed which was treated by irradiation. Later, a plastic operation was done on the nose. The patient was last seen March 15, 1946, at which time she was quite well except for moderate nervousness and weakness. There was no evidence of recurrence five years and nine months after abdominoperineal resection for carcinoma of the rectum. No change in blood pressure, cardiac rate, or consciousness could be elicited by pressure over the carotid sinuses. Blood pressure was 155 mm. systolic and 90 mm. diastolic.

CASE 3.—A 51-year-old, married, white man, a cab driver, was admitted to the Clinic on Nov. 1, 1942, complaining of attacks of dizziness and unconsciousness. He had been well until one year prior to his visit to the Clinic, at which time he had the first attack of dizziness and sudden unconsciousness. He was of a nervous disposition and during the past year had three attacks of dizziness and sudden unconsciousness. He could not associate the first two attacks with any particular movement but was certain the last one was associated with turning the head to the left quickly. While driving the cab he started to turn around at an intersection; as he looked backward over the left shoulder, he suddenly became unconscious and the cab ran into a pole. There was no incontinence, biting of the tongue, or convulsions. He recovered shortly and was taken to an emergency hospital where similar attacks of unconsciousness were reproduced by "pressure over the left side of the neck." He was not permitted to return to work. After a brief but unsuccessful trial with medical therapy he was advised by his physician to have surgical treatment.

Examination gave essential negative results. The heart was not enlarged. The blood pressure was 110 mm. systolic and 70 mm. diastolic; the pulse rate was 70. Laboratory studies of the blood and urine, including serum calcium and blood sugar determinations, were negative. The electrocardiogram was normal.

Pressure over the right carotid sinus resulted in slight change in blood pressure and cardiac rate. Pressure over the left carotid sinus caused a marked fall in blood pressure, slowing of the cardiac rate, pallor, dizziness, and unconsciousness. On Dec. 1, 1942, the left carotid sinus was denervated. He was discharged on the fifth postoperative day improved.

On the night of discharge from the hospital, the patient attended the theater and did not return home until late. The following morning, while shaving, he had a spontaneous attack of dizziness and unconsciousness. He fell to the floor but did not injure himself. His wife stated that when she reached him he was pale and perspiring, but was having no convulsive movements. There was no incontinence or biting of the tongue. He regained consciousness in about four minutes but was disoriented and not aware of what had happened. Examination on the following day at the Clinic gave negative results. The incision over the left side of the neck was healing per primam. Compression of the carotid sinus on either side did not result in syncope. When the history was reviewed, he admitted, for the first time, that some thirty years before, when he was 19 years of age, he had a seizure during which he lost consciousness for a few minutes. He denied any attacks of vertigo, syncope, or convulsions during the thirty-one year interval between this seizure and the onset of the present illness. He was referred to the neurologic department for further study. Roentgenologic studies of the skull were negative. An electroencephalogram was done at the Boston Psychopathic Hospital and reported as follows: abnormal encephalographic report—record consistent with vulnerable cortex and epileptic dysrhythmias. Neurologic examination was negative except that he was apprehensive and nervous. The neurologist believed that he was not an epileptic and that he did not have a brain tumor. Because of the nervousness he was placed on small doses of phenobarbital daily. After a short period of observation he was permitted to return to his job as a cab driver.

The patient was last seen May 10, 1944, eighteen months following operation, at which time he was feeling well except for nervousness and an occasional attack of dizziness. There had been no syncope, unconsciousness, or convulsions. No changes could be elicited by pressure over the carotid sinuses. Blood pressure was 130 mm. systolic and 82 mm. diastolic.

COMMENT

Case 3 is particularly interesting. In view of the rather atypical history and seizures, the patient was not considered to be an epileptic. Robinson[13] has made an interesting study to determine the incidence of hypersensitive carotid sinus reflex among 1,000 cooperative institutional patients with epilepsy. In every instance, syncope, convulsions, or transitory loss of consciousness had brought the patient to the hospital. Of the 1,000 patients examined, 9 had a

hypersensitive carotid sinus reflex, an incidence of 0.9 per cent. In five cases a hyperirritable reflex seemed to be the sole mechanism underlying all seizures —spontaneous and induced. Three patients had hyperactive carotid sinus reflexes and were also known to have an additional convulsive mechanism.

The anesthetic management of the hyperactive carotid sinus has been well presented by Rovenstine and Cullen,[14] and Ruzicka and Eversole.[15] Although this discussion pertains primarily to the surgical treatment of the hypersensitive carotid sinus, the surgeon as well as the anesthetist should be aware of the reactions that may occur from an apparently normal sinus which has been sensitized.[6, 15] It should be emphasized that an apparently normal carotid sinus may be sensitized by various drugs[6, 7] (morphine, digitalis, thyroid extract), anesthetic agent[14, 21] (light anesthesia, nitrous oxide, evipal), or surgical procedure[21] (operation on the neck). During an operation, a patient without previous evidence of an abnormal carotid sinus may suddenly exhibit alarming signs, such as pallor, bradycardia, arrhythmia, asystole, hypotension, and apnea. Reactions occur most often during operations on the neck and death may result suddenly. Such deaths are often said to be the result of circulatory failure. When such a carotid sinus reaction occurs, treatment must be started immediately. The head should be lowered, oxygen administered, packs and retractors removed, and 3 to 5 c.c. of a 2 per cent solution of procaine hydrochloride infiltrated at the area of the bifurcation of the common carotid artery,[14] Stimulants and fluids are of no value.

In a study of the surgical anatomy of the carotid sinus, Sheehan, Mulholland, and Shafiroff[17] found that the principal nerve supply to the sinus was through the glossopharyngeal nerve by way of the carotid sinus nerve (nerve of Hering). They concluded that "the anatomy suggests the feasibility of dividing the carotid sinus nerve in preference to extensive stripping of the carotid artery in the surgical treatment of carotid sinus syncope." It has also been shown by Code, Dingle, and Moorhouse[4] that the cardiovascular components of the sinus reflex are conducted solely through the carotid sinus nerve. Ray and Stewart's[12] observations, however, indicate that the glossopharyngeal nerve in man is not in every instance the only nerve through which afferent impulses of the carotid sinus reflex are transmitted. Anatomically, it may be feasible to section only the carotid sinus nerve in the treatment of carotid sinus syncope. We believe that the surest way of denervating the sinus is by section of the carotid sinus nerve and extensive stripping of the common, internal, and external carotid arteries. Immediately after denervation of the sinus an increase in the blood pressure and heart rate occurs. This is only transient[23] and it has been shown that, in man, hypertension and tachycardia following even bilateral denervation rarely last as long as a week.[3]

Treatment of the carotid sinus syndrome may be medical or surgical. Those patients in whom the symptoms are mild and the attacks occur infrequently may require no treatment as they can be managed by reassurance and conservative measures. If possible, fatigue, worry, and emotional upsets should be eliminated. They should be advised to avoid turning the head quickly,

looking upward, or stooping suddenly. Any constriction about the neck should be avoided. Should the attacks, even though mild, occur with increasing frequency, medical treatment should be instituted. Many drugs have been used—phenobarbital, ephedrine, atropine, benzedrine, and so forth—but have not been particularly satisfactory.[5, 12] A number of patients may be helped by excision of inflammatory or neoplastic cervical glands, by antisyphilitic therapy, or by diminishing the dose in digitalis therapy. Stevenson[19] has suggested x-ray irradiation of the carotid sinus as suitable treatment for the hypersensitive reflex. We have had no experience with this form of treatment. Surgical treatment is indicated in: (1) those patients in whom the symptoms are severe and incapacitating, thus preventing them from carrying out their usual occupation, (2) those in whom medical therapy has been unsuccessful either because of poor response to medication or because of drug intolerance, and (3) usually those in whom the mixed or cerebral type of response is presented.

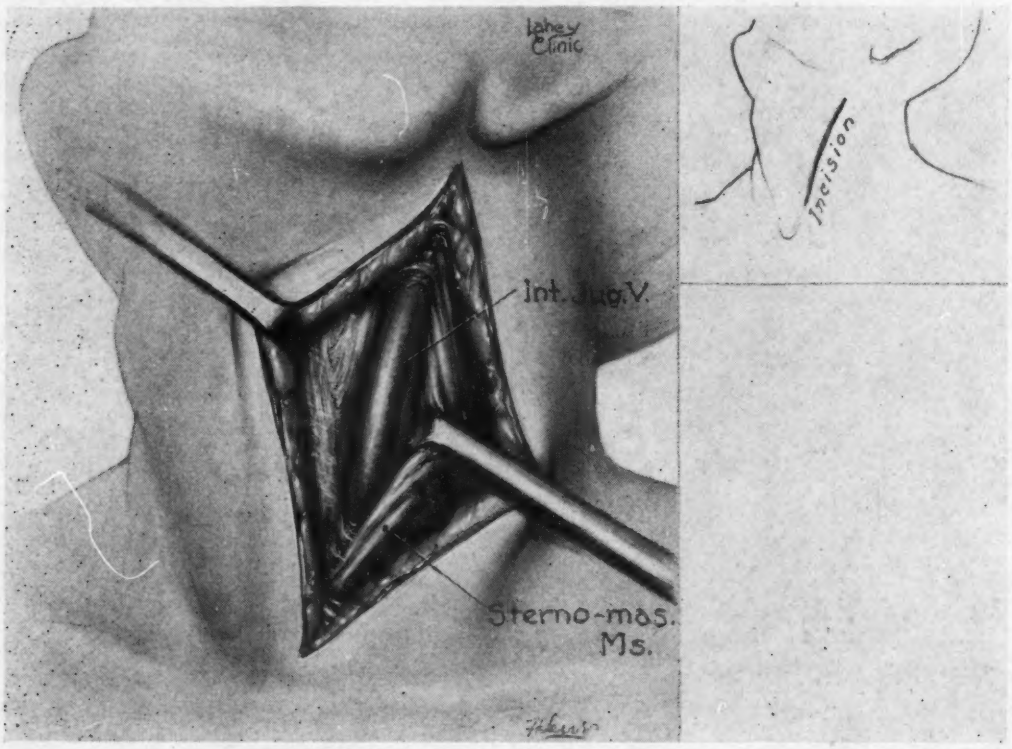

Fig. 1.—The sternomastoid muscle has been retracted laterally and the carotid sheath opened, exposing the internal jugular vein. Insert shows location of incision.

The operation consists of stripping the common, internal, and external carotid arteries at the bifurcation, sectioning the carotid sinus "nerves," and removing the intercarotid tissue. Endotracheal cyclopropane and ether anesthesia are recommended. These may be supplemented by procaine block in the very hyperactive carotid sinus to prevent serious disturbances in pulse and blood pressure.

With the patient in the supine position, the head is rotated laterally and the neck slightly extended, exposing the side to be operated upon. The skin is prepared and the neck draped in the usual manner. An incision 8 cm. long is made along the anterior border of the sternomastoid muscle centered at the level of the upper border of the thyroid cartilage (Fig. 1). The incision

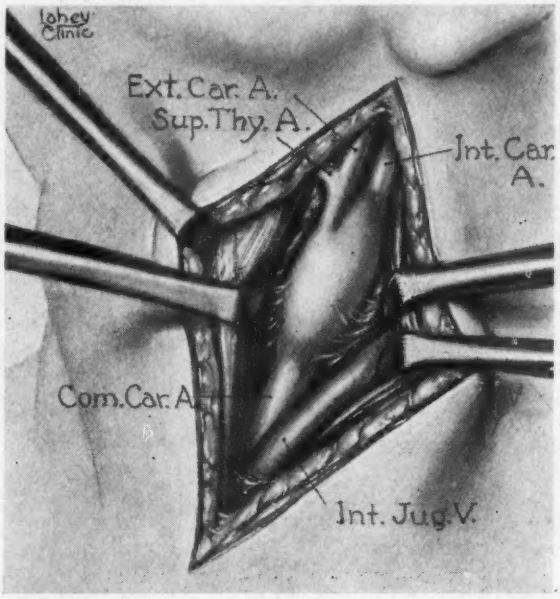

Fig. 2.—The dissection is continued and the internal jugular vein freed and retracted laterally with the sternomastoid muscle, exposing the carotid sinus, the common, internal, and external carotid, and superior thyroid arteries.

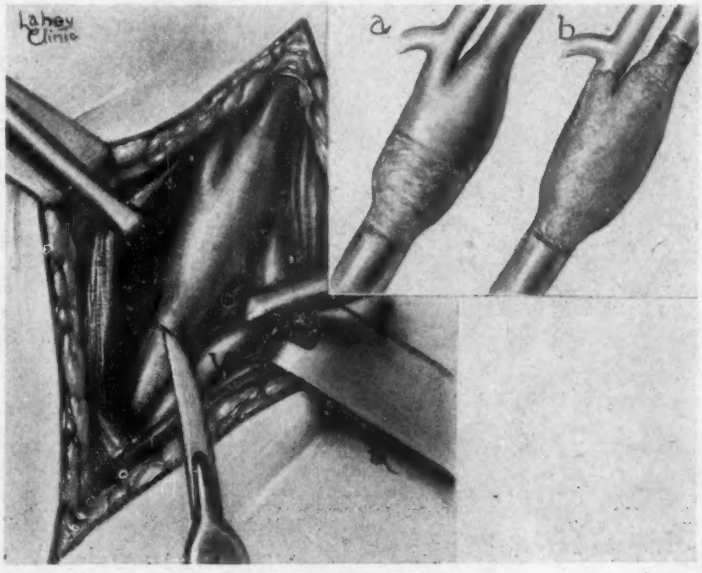

Fig. 3.—The common, internal, and external carotid arteries have been completely freed. The carotid sinus is denervated by periarterial stripping of the adventitia (see text). Insert *a* and *b*: The periarterial stripping is started below and carried well above the bifurcation of the common carotid artery.

is carried through the skin, platysma, and superior cervical fascia to the sternomastoid muscle. Retraction of the sternomastoid muscle laterally exposes the carotid sheath containing the internal jugular vein, carotid artery, and vagus nerve (Fig. 1). The carotid sheath is entered carefully so as not to injure the contents or the hypoglossal nerve which lies on its surface (Fig. 2). With the internal jugular vein and the sternomastoid muscle retracted laterally, the common, internal, and external carotid arteries are exposed and the adventitia stripped by sharp dissection for at least 2 cm. above and below the bifurcation (Fig. 3). If difficulty is encountered in the periarterial stripping, it may be facilitated by using a small syringe and fine needle and injecting normal saline solution beneath the adventitia, thus separating it from the media. The intercarotid tissue, which contains many nerve fibers and the carotid body, is freed laterally and inferiorly from the bifurcation and divided well above it. When the intercarotid nerve is sectioned, an increase in the blood pressure and heart rate occurs, indicating that the reflex arc has been broken. The wound is closed in layers.

No special postoperative care is necessary. The patient is allowed out of bed on the second postoperative day and may be discharged any time thereafter.

SUMMARY

The physiology, clinical manifestations, and diagnosis of the carotid sinus syndrome have been reviewed briefly.

Mention is made of the reactions which may occur during an operation from an apparently normal carotid sinus.

Treatment of the carotid sinus syndrome is briefly discussed.

Three cases are presented.

Carotid sinus syncope may be relieved by surgical denervation of the sinus.

A technique for carotid sinus denervation, which has been satisfactory in this Clinic, is presented.

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THE TREATMENT OF CAUSALGIA ARISING FROM GUNSHOT WOUNDS OF THE PERIPHERAL NERVES

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THE development of intractable pain and trophic disturbances following gunshot wounds of the extremities, particularly those involving the peripheral nerves, has long been recognized. To this syndrome the term causalgia was applied by Mitchell, Morehouse, and Keen[1] in 1864. By the use of this term, attention was called to the "burning" character of the pain of which the patient frequently complained.

The incidence of this condition is expectedly greater in time of war when so many casualties with wounds of the sensitive structures come under observation. Spiegel and Milowsky[2] described in detail nine individuals observed in a series of 275 cases of unselected peripheral nerve injuries. Mayfield and Devine[3] encountered fifteen cases of severe causalgia in a group of 737 peripheral nerve injuries, an incidence of 2 per cent. In civilian life this condition is not rare. Miller and de Takats[4] have emphasized the frequency with which some form of causalgia-like pain may be observed in all injuries.

Early recognition of causalgia is important, not only because there are now available means of giving relief of the pain, but especially because if this condition is allowed to continue, severe and crippling deformities may result.

The characteristic feature of causalgia which serves to differentiate it from other forms of pain is that it always responds dramatically, even if only temporarily, to the interruption of the nervous pathways which course through the sympathetic ganglia supplying the segment. There are other features such as disturbances in sensation, deep pressure pain especially in the muscles of the extremity, reflex paralysis, dyskinesia on attempting voluntary movements of the part, and the vasomotor and trophic disturbances, but these accessory observations are not uniform. The single constant finding is the response of the pain to the injection of procaine into the region of the paravertebral sympathetic ganglia.

Many theories have been advanced to explain the mechanism of this pain. According to Leriche[5] the afferent pathway is through the sympathetic fibers, both those contained in the mixed nerves and those in the perivascular nerve plexus. Laboratory investigations, in the main, have failed to demonstrate the presence of afferent fibers from the extremities in the sympathetic nerves or ganglia, although Kuntz and his associates[6, 7] have reported evidence, both anatomic and physiologic, of the presence of such sensory pathways in the experimental animal. Pereira[8] has recently presented additional evidence that affer-

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ent fibers from the perivascular plexus in man traverse the sympathetic ganglia. Lewis[9] has advanced the concept that efferent discharges of sympathetic impulses produce anoxia through vasoconstriction and that the afferent pathway is mediated through a set of hypothetical "nocifensor" nerves. This explanation simply acknowledges the fact that increased sympathetic activity is frequently observed and that blocking the sympathetic nerves relieves the pain but fails to identify the essential afferent mechanism. According to Livingston,[10] the dysfunction of the sympathetic nerves is but one part of a more profound alteration of the physiologic status of the spinal cord centers.

Recent experimental work of Granit, Leksell, and Skoglund[11] has demonstrated that an artificial synapse is produced in a mixed nerve by injury or pressure. In the presence of such a zone of localized trauma centrifugal impulses give rise to centripetal action currents. They suggested that these findings might be of significance in explaining the mechanism of certain obscure types of pain. Doupe, Cullen, and Chance[12] have used this concept to explain the production of causalgia. In a series of patients who were carefully studied they showed that the pain was aggravated by any stimulus which called forth activity of sympathetic nerves and that it was ameliorated by conditions in which sympathetic activity was inhibited. According to their observations efferent discharges over sympathetic pathways traversed the artificial synapse at the site of injury and in this way produced impulses in afferent nerves which resulted in the sensation of pain. They also confirmed an observation originally made by Tinel[13] that relief of pain in certain cases of causalgia might be produced by blocking the nerve distal to the point of injury. On the basis of the presence or absence of relief from suppression of impulses in the peripheral region of the nerve they classified their cases into the "distal" and "proximal" causalgic syndrome.

The present communication is based on a study carried on over a period of fourteen months, of 114 cases in which the diagnosis of causalgia was made. These cases were selected on the basis of diagnostic tests from 2,167 casualties with wounds of the extremities, an incidence of approximately 5 per cent. In only twenty of these cases, however, was the causalgia classified as severe. The patients were Chinese soldiers who were cared for in a U. S Army General Hospital. The casualties were received by air evacuation usually two to three days after they had been wounded. Their injuries had generally been treated in the forward area by débridement and plaster fixation at one of the portable surgical units or field hospitals. The patients were admitted to the general surgical service and these observations on causalgia were made during the day-by-day surgical management of the cases.

The Chinese soldier is especially suited to a study of subjective sensations. He is generally intelligent and cooperative. He is rarely neurotic. Although brave and accustomed to enduring hardships and privations he is not hesitant to show by word, facial expression, and gesture that he is suffering pain. Above all, it is not part of his philosophy to minimize his complaints even to gratify the medical officer who is caring for him and to whom he may be sincerely at-

tached. The language barrier is, if anything, a help in arriving at an impartial evaluation of the results of treatment since the interpreter assumes the post of middleman venerated by centuries of tradition as an impartial judge.

Because of modern methods of treatment of wounds in the forward areas by excision of devitalized tissues and immobilization, together with chemotherapy, casualties are generally free from pain after the first few days unless infection or tissue ischemia are present. Passive movement of the extremities should not cause pain unless such a manipulation directly disturbs the injured tissues. Those patients should be suspected of causalgia whose complaints are out of proportion to the severity of their wounds, especially if the pain is greatly increased by passive movement.

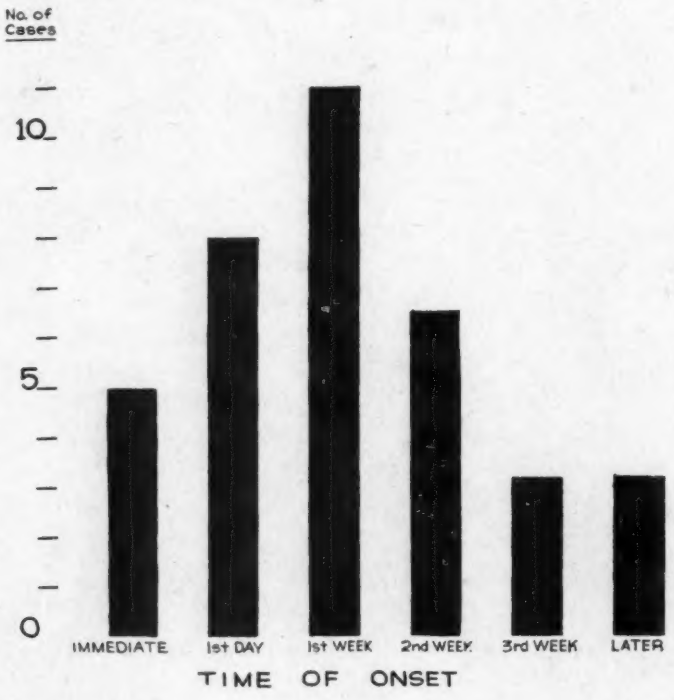

Fig. 1.

Character of Pain.—Although the pain of causalgia is characteristically described as burning in quality, out of a series of forty-two patients who were specifically asked to characterize their pain, only seven applied this term to it. Thirty-one described it as "numb" in character and an additional four as "sticking" or "stabbing." The pain was generally worse at night. Only four patients claimed that it was worse in the daytime. In two-thirds of the group the symptoms were increased by wet weather but there was no significant change noted with variation in temperature.

Onset.—In Fig. 1 the time of onset of the pain is analyzed. In a few patients the pain came on immediately after injury; in a larger number, within the first day. The majority of patients developed pain during the first week

and the incidence then decreased. It was interesting to note that in two patients the characteristic pain did not come on until as long as six weeks after the initial injury.

Examination.—The diagnosis of causalgia in the severe case can frequently be made at first glance. Fig. 2 illustrates the typical appearance of the patient suffering from severe causalgia. The face is drawn with pain and the affected part zealously guarded from any movement or stimulation.

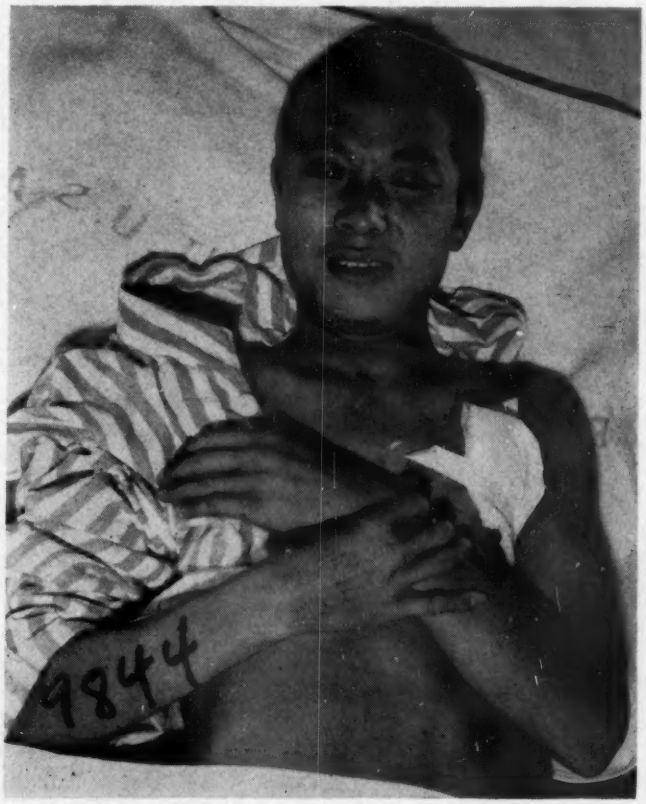

Fig. 2.
(Courtesy of Museum and Medical Arts Service, U. S. Army Medical Museum.)

The patient's entire attention is absorbed by the pain and he is indifferent to surroundings. Any movement, jarring of the bed, or even noise produces aggravation of the pain so that he is in constant misery. Only five patients in the present series kept the hand wrapped in a wet cloth but frequently the patients shielded the extremities with bedclothes or garments. Voluntary movements of the extremity were effected slowly and with a curious jerking quality suggestiong dyskinesia. Passive movements, even when performed slowly, were associated with sudden muscular resistances. The muscles, however, did not feel to be in spasm. Sensory examination revealed diffuse hypoesthesia and hypalgesia which frequently spread far beyond the anatomic region of the injured nerve. Deep pressure, especially of the muscles, was painful.

Vasomotor and Trophic Disturbances.—Early in the course, vasomotor changes were quite variable. Skin temperature and oscillometric readings were usually within normal limits. Only after weeks did the characteristic trophic changes occur. These abnormalities generally consisted in thickening of the skin with piling up of the epidermis, long hair, and atrophic nails. These disturbances appeared to be due chiefly to lack of use. Of more serious significance were the soft-tissue changes, especially about the joints of the hand. With prolonged pain and immobilization these joints became so stiff that the hand was frequently useless even when the pain had subsided. It was my experience that the Chinese soldier was generally not benefited by even the most painstaking treatment in the physiotherapy department. If movement caused pain, he just refused to move the affected part. The results were necessarily discouraging but furnished an even greater stimulus toward devising some form of treatment which, by abolishing the pain, would allow the individual to use the part.

Paravertebral Injection of Procaine.—The diagnosis was confirmed in every case by the clinical response to temporary interruption of nervous impulses traversing the sympathetic ganglia. For the lower extremity, 20 c.c. of 2 per cent procaine containing 2 drops of 1:1,000 adrenalin were injected into the region of the second lumbar ganglion. With the patient lying on his side a four-inch No. 22 gauge needle was inserted through the skin in the depression between the lower border of the twelfth rib and the paravertebral muscles. The needle was advanced at a 60 degree angle from the horizontal, using small amounts of ½ per cent procaine to infiltrate the superficial tissues, until contact was made with the body of the vertebra. The point of the needle was then advanced by successively withdrawing and depressing the hub during reinsertion until the point could be felt just gliding past the anterolateral surface of the lumbar vertebra. With the needle in contact with bone the solution was *slowly* injected.

For the upper extremity 15 c.c. of the procaine solution was injected by the anterior approach. With the patient recumbent and the head turned to the opposite side the scalenus anticus muscle was defined by palpation just lateral to the clavicular head of the sternocleidomastoid muscle. A point one inch above the clavicle was marked. After the skin and deeper tissues were infiltrated, a No. 22 gauge needle, 2½ to 3 inches long, was inserted at a 45 degree angle between the horizontal-sagittal and the sagittal-coronal planes of the body. At a depth of 1½ to 2 inches, contact was made with bone. Five cubic centimeters of solution were *slowly* injected. With rapid rates of injection serious reactions have been observed. The needle was then partially withdrawn and again inserted slightly caudalward so as to have the point pass over the head of the first rib. When once more in contact with bone, 10 c.c. of the procaine solution were injected. In this series of cases 211 paravertebral injections of procaine were given. A pneumothorax developed in five patients although in only one case was it necessary to aspirate the air from the chest. There were no other serious reactions. Because of fatalities which have been reported during the injection of procaine into the paravertebral region, it is necessary to re-emphasize the fact that the procaine must be injected slowly. The rate of injection should never

exceed 5 c.c. in one minute. Within five or at most ten minutes, signs of paralysis of the sympathetic nerves should be apparent. Flushing of the skin, dilatation of the veins, and cessation of sweating are generally observed in that order. Increased warmth from arterial dilatation is slower in coming on. In addition, Horner's sign should be present when the thoracic ganglia are blocked.

The pain of causalgia frequently disappears even before signs of sympathetic paralysis are observed. With the cessation of pain the ability to move the part is increased. The deep muscle tenderness usually persists and pain is evoked on any attempt to manipulate stiffened joints. But the striking feature of causalgia is the disappearance of the pain even though the sensory and motor nerves are unaffected by the injection. This relief may last only as long as the effect of the procaine or it may persist for hours and even days. In the mild cases the pain may be permanently relieved by one or more injections.

TABLE I

UPPER EXTREMITY		LOWER EXTREMITY	
Brachial plexus	11	Sciatic	5
Median	15	Posterior tibial	6
Radial	18	Peroneal	5
Ulnar	13	Cutaneous	2
Cutaneous	3	Foot	3
Digital	25	Joints	1
Blood vessels	3		
Joints	4		
Total	92		22
Total cases	114		

Structures Involved.—Causalgia has been reported most frequently after lesions of the median and sciatic nerves. In Table I is presented an analysis of the structures involved in this series of cases. This condition may apparently come on after injury to any sensitive structure. The severe cases, however, were seen only after injury of the brachial plexus, median, radial, and ulnar nerves and, in the lower extremity, the sciatic nerve. Contusion or incomplete severance of the nerve was generally found when the lesion involved one of the major nerves. Pain following hand injuries which could be benefited by paravertebral procaine injection was frequently associated with complete division of one of the digital nerves.

TREATMENT

Since such striking relief was obtained from temporary interruption of the nerve impulses traversing the sympathetic ganglia and since lasting relief has been reported by Homans[14] with repeated injections, this form of therapy was first tried. It was disappointing to find that only mild cases of causalgia responded to one or even repeated injections. Even though there was temporary improvement, relief did not persist. As many as eight injections were given in a single case without permanent benefit.

Preganglionic sympathectomy was then used for pain in the upper extremity in two patients. The sympathetic chain was divided below the third thoracic ganglion and the connections between the second and third ganglia and

the spinal cord were severed. Prompt relief was observed but within one week the characteristic pain had returned. Although not as severe as before sympathectomy it still prevented full use of the hand and, above all, soft tissue changes were not prevented.

On the basis that preganglionic section of the sympathetic supply to the upper extremity might not sever all the connections which were responsible for the development of pain, resection of the ganglia including the stellate was then performed in four cases. Although the results were excellent in two cases, only moderate improvement was obtained in the third case and in one patient, although immediately after operation he was completely relieved, within one week there was definite recurrence of the pain. Clearly, some other form of treatment was needed.

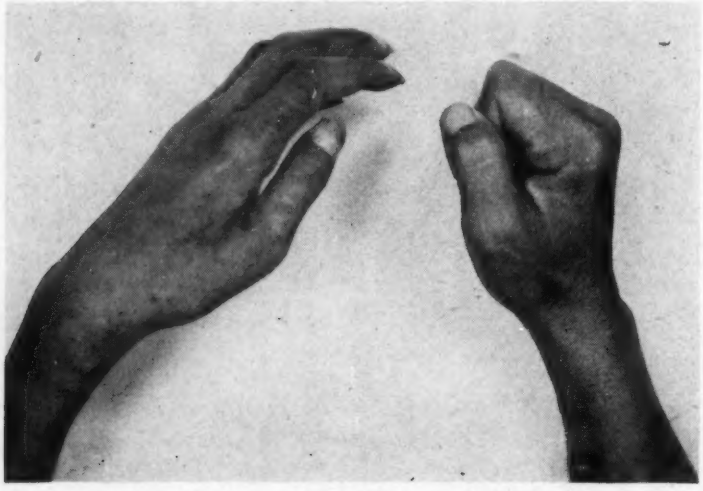

Fig. 3.
(Courtesy of Museum and Medical Arts Service, U. S. Army Medical Museum.)

It was noted at this time that the symptoms of causalgia were more effectively relieved by injection in those cases in which the extremity had been immobilized in plaster because of a coexistent fracture. Twenty-one patients were accordingly treated by immobilization in plaster with repeated paravertebral injections of procaine. Only ten of them obtained lasting relief and these were generally mild cases of causalgia. The end results as far as function was concerned were poor. Many of the patients developed marked soft tissue changes in their hands with stiffening of the joints of the fingers. Fig. 3 illustrates the useless hand produced by long-standing pain and disuse.

On the basis that Leriche[5] had obtained encouraging results in the treatment of causalgia from periarterial sympathetctomy a more radical type of operation was used. Through the anterior supraclavicular approach the stellate second and third thoracic ganglia with the intervening chain were resected and, in addition, the adventitia with its plexus of nerves was stripped from the subclavian artery. This operation was followed by consistent relief of pain. It was used at first only in the long-standing intractable cases in which all other forms

of treatment had been attempted. Seven patients who had had severe pain for from three to six months were subjected to this radical operation. Although the pain was relieved in each case, in only two was there recovery of function. In the other five, although the pain was relieved, the soft tissue changes associated with months of disuse precluded normal function. Fig. 4 illustrates the type of useless hand so often encountered. It is significant that no patient in whom the diagnosis of moderate or severe causalgia was made during the first part of this study was returned to duty.

A casualty was admitted to the ward in July, 1944, who had sustained a partial lesion of the brachial plexus from a shell fragment. He was suffering such intense pain that radical sympathectomy appeared to be the only form of treatment which would give lasting relief. He was operated upon ten days after the initial injury. Upper thoracic ganglionectomy and periarterial sympathectomy of the subclavian artery were performed. Not only was the pain permanently relieved but he did not develop any of the secondary changes of fibrosis, thickening of the skin, or contractures. Fig. 5 shows the flexibility of his soft tissues.

Fig. 4.
(Courtesy of Museum and Medical Arts Service, U. S. Army Medical Museum.)

In the succeeding ten cases of moderately severe and severe causalgia, paravertebral injection of procaine was used for diagnostic purposes only. The patient was then subjected to early, radical sympathectomy. Relief of pain was obtained in all cases. The functional results were excellent. Crippling deformities from contractures and soft tissue changes were prevented. It is significant that of the ten patients treated by early radical sympathectomy eight were returned to light duty. Even though the paralyses associated with the nerve lesions persisted, the patients had no pain and had free movement of the extremities.

There still remained the lesion of the peripheral nerve which required treatment for restoration of function. According to the prevailing opinion at

the time the earlier cases were being studied, suture or lysis of the peripheral nerve had been delayed until healing of the wound was complete. The report of Churchill,[15] however, indicated that, with the use of penicillin, early secondary closure of wounds could be undertaken. Provided that no devitalized tissue or infection was present the wounds could best be closed between the fourth and tenth day after injury. This reparative surgery offered an ideal opportunity for removing the initiating factor which was producing the causalgia, namely, the irritation of the injured nerve.

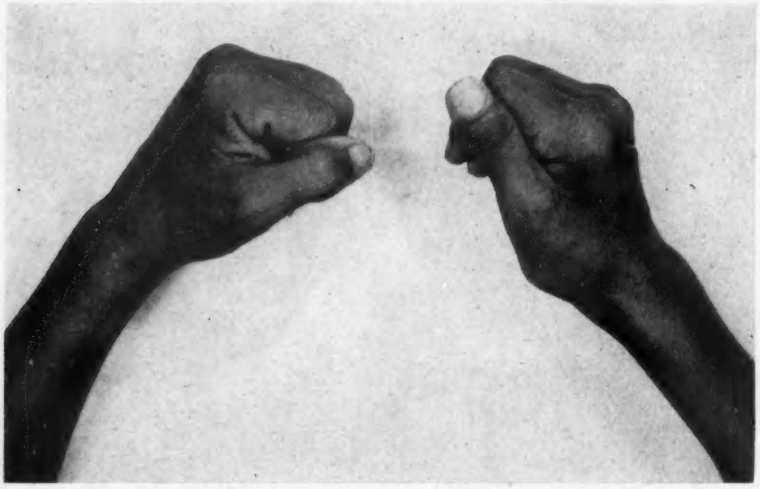

Fig. 5.
(Courtesy of Museum and Medical Arts Service, U. S. Army Medical Museum.)

Four patients with causalgia were treated by this method. They were all suffering severe pain. The diagnosis of causalgia was confirmed by the temporary relief afforded by paravertebral injection of procaine either before or after operation. Penicillin, by the intramuscular route, was adminsitered, 15,000 units every three hours, starting the day before operation and continued for three days afterward. In the operating room the fresh wounds were widely opened, all devitalized tissues excised, and the injured nerves sutured. The wounds were closed without drainage. Postoperative injections of procaine into the region of the sympathetic ganglia were needed in only two of the cases. After wound healing, complete freedom of movement was preserved in each of the cases without the development of any fibrosis or soft tissue changes about the joints.

CASE REPORTS

CASE 1 (15937).—The patient was a Chinese soldier who sustained a perforating wound of the right wrist from a rifle bullet on Feb. 3, 1945. Débridement of the wound with immobilization in plaster had been performed in the forward area. At the time of admission, four days later, he was suffering from severe pain in the hand and this pain was increased by any form of stimulation. Beginning flexion contracture of the fingers was already apparent and any attempt at passive movement was associated with severe pain. Paravertebral injection of procaine was followed by dramatic relief of pain which lasted for three hours. Nine days after injury he was taken to the operating room and, under anesthesia, the plaster cast

was removed. The wound was found to involve the anterior surface of the wrist on the ulnar side two inches above the joint. The severed ends of the flexor muscles and tendons protruded into the wound. The ulnar nerve was found to be partially divided and bound by plastic exudate to the traumatized muscles. A secondary débridement was performed, excising the remaining devitalized tissues. The traumatized segment of the ulnar nerve was excised. The tendons were then sutured and the fresh-cut ends of the nerve approximated. The wound was closed without drainage. The wrist was put in acute flexion with a posterior plaster splint. The patient was completely relieved of pain from the time of operation. Passive movement of the fingers no longer caused him to wince. When the wound was healed, complete freedom of movement was preserved although anesthesia in the ulnar distribution and paralysis of the intrinsic muscles of the hand supplied by the ulnar nerve persisted.

CASE 2 (16006).—A Chinese soldier was wounded in the upper third of the right arm by a rifle bullet on Feb. 2, 1945. The wound of entrance was over the mesial surface of the arm three inches below the axillary fold and the wound of exit was on the posterolateral surface of the arm at the same level. Immediate paralysis of the upper extremity had occurred. After superficial débridement of the wounds he had been admitted to an evacuation hospital in the forward area. On February 10, eight days after injury, he suddenly developed a marked increase in the swelling of the arm with severe pain. The diagnosis of pulsating hematoma was made and he was evacuated to the general hospital. Upon admission he was taken immediately to the operating room. Under general anesthesia the brachial artery was exposed just below the axilla and encircled with a segment of rubber tubing. The incision was then extended to open the wound widely. The fresh blood and clots were evacuated and the laceration of the wall of the brachial artery was exposed. Since the wound of the artery was below the origin of the profunda and since the wall of the artery was contused, repair was not attempted. The artery was divided and both ends ligated. Complete exploration of the wound was then performed. The median nerve was found to be completely divided and the ulnar nerve partially severed. It would have been impossible to approximate the ends of the nerves in case that the traumatized region had been excised. Accordingly a "bulb-suture" of the nerves was performed and the wound closed without drainage. Although the circulation to the hand was quite adequate, the patient complained of severe pain following operation. This pain was completely and permanently relieved by a single paravertebral injection of procaine. Neurorrhaphy of the median and ulnar nerves was performed on March 8, five weeks after the original injury. The complete freedom of movement and absence of pain on manipulation persisted and the patient was discharged to a convalescent hospital without any soft tissue changes or contractures.

CASE 3 (16072).—This patient was struck on Feb. 2, 1945, by a shell fragment over the insertion of the deltoid on the right side. The fragment apparently split and one of the particles passed anterior to the humerus with the wound of exit in the posterior axilla while the other passed posterior to the humerus and lodged in the thorax. He was kept in the forward area for seventeen days because of the hemothorax. At the time of admission he presented evidence of complete paralysis of the radial and musculocutaneous nerves. He was suffering from severe pain which was completely although temporarily relieved by paravertebral injection of procaine. Five days after admission, some three weeks after wounding, while the wounds were in the process of healing, complete exploration was carried out. The radial nerve was found to have been severed by the fragment which passed to the posterior side of the humerus while the musculocutaneous was found to have been divided anterior to this structure. End-to-end sutures were performed after excision of the damaged portions of the nerves. After operation, two paravertebral injections were required to produce complete and permanent relief of the pain. Although the paralysis persisted there was no subsequent limitation of motion of the hand or fingers.

CASE 4 (16199).—A patient on Feb. 20, 1945, had sustained a laceration from a sharp piece of bamboo across the anterior surface of the left wrist on the ulnar side, one inch above

the joint. Immediate primary suture of the wound had been performed in the forward area. The operative note which accompanied the patient stated that a suture of the divided ulnar nerve had been performed. At the time of admission on March 5, the wound was clean and the skin healed. The stitches had been removed before admission. The patient complained of severe pain and there was already a beginning flexion contracture of the fingers. Temporary relief was afforded by paravertebral injection of procaine. The following day he was anesthetized and the healing wound was widely opened. An anomaly of the ulnar nerve was disclosed in that the nerve was found to divide approximately three inches above the wrist. Only one of the division had been sutured and the nerve at this point was adherent with plastic exudate to the edematous muscle and fascia. The devitalized portions were excised and the fresh ends of the two nerves were approximated. The wound was resutured without drainage and the wrist maintained in acute flexion with a posterior plaster splint. Complete and permanent relief of pain was afforded.

DISCUSSION

Recently published studies[2, 3] on the cases of causalgia resulting from gunshot wounds of the nerves incurred in World War II have come from general hospitals in the Zone of the Interior. The incidence of severe causalgia in nerve injuries has been given as from 2 to 3 per cent. In the present series, the incidence in 2,167 unselected cases of gunshot wounds of the extremities was 5 per cent, although the severe cases amounted to less than 1 per cent. It is probable that the pain in many of the milder cases included in this study would have subsided spontaneously. It was only because an active search was made for cases of pain that were amenable to relief by blocking the sympathetic nerves that as large a group was found. Miller and de Takats[4] have reported a similar high incidence of causalgia-like pain after injuries in civilian life. It is likely that an even larger percentage of cases of trauma would have a causalgic component to the pain if appropriate studies were made.

A considerable period of time generally lapses between the initial injury and the time that the casualty arrives in a hospital in the Zone of the Interior in which definitive surgery can be carried on and completed. Although numerous studies have been carried out on patients who have had the pain for some months and in whom trophic changes and fibrosis of the soft tissues have already taken place, it is believed that the present series of cases is unusual in that the casualties were observed shortly after they had received the injuries and before the secondary changes could take place. An opportunity was thus afforded of instituting treatment at the earliest possible moment in order to prevent the development of irreversible damage to the soft parts. In addition, daily contact with the patient during the period immediately after wounding, observation of the effects of treatment on the pain, and, above all, the opportunity of inspecting at the operating table the fresh lesion responsible for the production of the pain have permitted a closer insight into the pathogenesis of causalgia.

The dramatic relief of pain produced by the injection of procaine into the region of the sympathetic ganglia suggests that the nerve elements responsible for the perception of the pain are being anesthetized. The patients will frequently state that the extremity feels "numb" immediately after the block and yet neurologic examination fails to reveal any additional loss of sensation other than that due to the initial nerve injury. In fact, the extent of the hypoesthesia

may actually be decreased. It is as though the center were being bombarded by a multitude of pain impulses. Sudden cutting off of a large number of these stimuli leaves the part temporarily numb. Although clinical observations have strongly indicated the "sympathetic" origin of causalgia, as Leriche[5] was the first to point out, carefully controlled laboratory experiments in animals generally have failed to provide evidence for the transmission of afferent stimuli through the sympathetic ganglia. Only the observations of Kuntz and his associates[6, 7] have demonstrated such pathways. Livingston[10] has recently reviewed the experimental evidence and has concluded that "it is not reasonable to ascribe the benefit conferred by sympathectomy in the causalgic states to an interruption of pain pathways."

A recent concept which is more in keeping with the clinical findings is that supported by Doupe, Cullen, and Chance.[12] They adhere to the sympathetic origin of the pain of causalgia but attribute the stimuli to impulses coming down the efferent sympathetic fibers in the mixed nerves. At the artificial synapse produced in the area of injury,[11] these efferent impulses are believed to spread to the sensory afferent nerves and are then carried over the dorsal roots to be perceived as pain originating in the distribution of the injured nerve. This explanation does not explain the diffuse character of the pain of causalgia nor its peculiar burning quality. However, they present considerable evidence to support this concept. In one patient with causalgia of the foot, low spinal anesthesia sufficient to block the sensory roots to the part but not high enough to affect the efferent sympathetic fibers, as shown by the failure of the skin temperature to rise, was sufficient to abolish the pain. This experiment was cited as evidence that all pain sensations were ultimately transmitted by way of the dorsal roots supplying the segment. On the other hand, it is well recognized that the pain of causalgia may persist in spite of extensive rhizotomy. The following case is cited to raise again the question, "Is the sensation of pain from the extremities in man carried by somatic nerves alone?"

CASE 5 (16149).—A Chinese sergeant, was wounded in the left foot on July 25, 1944. For the following six months he was treated in a hospital in the forward area for severe pain in the fore part of the foot. The pain was temporarily relieved on two occasions by paravertebral injection of procaine into the region of the lumbar sympathetic ganglia. Because of continued pain and tenderness, in November and December, 1944, all the peripheral nerves to the foot had been crushed in the lower part of the leg. The pain and tenderness on pressure persisted in spite of demonstrably complete anesthesia to pin prick over the skin of the entire foot. Subsequently, a cordotomy was performed at the level of the second thoracic vertebra without affecting the pain and tenderness. Upon admission to the general hospital neurologic examination revealed loss of sense of pain and temperature on the left side below the fourth thoracic vertebra and complete sensory loss in the left foot except that pain and tenderness on pressure persisted in the distal end of the foot. Injection of procaine into the region of the left lumbar sympathetic ganglia caused prompt disappearance of the pain and tenderness. Determinations of the skin temperature during and after the injection showed that there was no rise. This absence of rise in skin temperature was presumably due to the interruption of all efferent vasoconstrictor impulses by the previous crushing of the peripheral nerves. Periarterial sympathectomy was then performed on the femoral artery in the groin with almost complete relief of symptoms. Ten days later, since there was still slight recurrence

of pain on pressure, a second lumbar injection was given. The pain was again completely abolished and accordingly a lumbar ganglionectomy of the first to fourth lumbar vertebra was performed. No further improvement occurred.

It may have been that, in this case, the initiating factor for pain had "escaped into the higher centers" as Livingston[10] has suggested. On the other hand, the persistence of tenderness indicates more likely that there is some additional pathway which has not been interrupted.

This case is noteworthy for the fact that abolition of efferent vasoconstrictor impulses by crushing the peripheral nerves did not abolish the pain. In spite of the absence of tonic sympathetic impulses, demonstrable by no rise in skin temperature after lumbar block, the pain persisted and was relieved only by the injection of procaine into the region of the lumbar sympathetic ganglia. The partial relief afforded by periarterial sympathectomy suggests that the periarterial nerves may be in part a route for the transmission of the painful impulses. Pearse[16] has cited a case of causalgia which was not relieved by lumbar sympathectomy but at a subsequent time was relieved by periarterial sympathectomy of the femoral artery. Pereira[8] recently showed in man that pain from stimulation of the perivascular tissues is transmitted through the sympathetic ganglia. The improvement noted in the results obtained in the present series of cases when periarterial sympathectomy was added to the upper thoracic ganglionectomy is additional evidence of the significance of this pathway in the mediation of the painful impulses. Further evidence against the concept that efferent sympathetic discharges are responsible for the pain is afforded by the experience reported by Mayfield and Devine.[3] In the treatment of causalgia of the lower extremity by lumbar sympathectomy they observed that one case was not relieved by resection of the third and fourth lumbar ganglia. However, when at a second operation the first and second ganglia were also removed the pain was relieved.

Inspection of the wounds within ten days after injury has revealed that the damaged nerves are in contact with devitalized tissue and are adherent to surrounding structures by means of plastic exudate. It is readily understandable that any slight contraction of the muscles would produce stimulation of these sensitive exposed structures. To account for the persistence of the pain it is suggested that any stimulation which produces involuntary contraction of the striated muscle in the neighborhood of the injured nerve will produce pain. The pain impulses may be carried over the sensory fibers in the sympathetic system described by Kuntz and his associates.[6, 7] The pathways may be both in the mixed nerves and in the periarterial network. The afferent stimuli upon entering the cord may excite contraction of the muscles which supply the region of the injury and thus occasion further stimulation of the sensitive injured structures. Paravertebral injection of procaine by abolishing the painful stimulation may break up this vicious circle. If there is extensive partial injury to the nerve, recurrence of the vicious circle generally takes place spontaneously. With a mild injury, one injection alone may afford permanent relief. In the severe cases, the vicious circle can be prevented by shielding the area of injury through

accurate approximation of the exposed nerve ends. If this is impossible, complete severance of all pathways is necessary in order to abolish the reflex permanently.

Nothing more than a suggestion is possible as to the mechanism of causalgia. The hypothesis of the "sympathetic" origin of the pain in man is in accord with clinical experience. This hypothesis is not in accord with the majority of observations made on experimental animals. The therapeutic implications, however, are clear. It is essential to relieve the pain early before the onset of soft tissue changes. Recognizing the fact that the initial lesion is trauma to a nerve, generally incomplete severance of one of the large nerves of the extremities, prompt exploration with adequate débridement, and early closure of the wound are indicated. Persistence of pain can generally be abolished by one or more injections of procaine into the region of the sympathetic ganglia. Although radical sympathetic ganglionectomy, possibly combined with periarterial sympathectomy, will give relief from pain, it should be used only in the event that local repair of the nerve is impossible because of complicating factors, or that the pain persists in spite of repeated paravertebral injection. Sympathectomy should be performed as soon as it becomes apparent that treatment of the local lesion will not afford relief from pain.

SUMMARY

The diagnosis of causalgia was made on the basis of the relief of pain by paravertebral injection of procaine in 114 Chinese casualties selected from 2,167 cases of gunshot wounds of the extremities. The causalgia was severe in twenty of these cases.

Permanent relief of pain following sympathetic block by paravertebral injection of procaine, even when repeated, was obtained only in the mild cases.

Partial recurrence of pain was noted in four out of six cases following preganglionic sympathectomy or ganglionectomy.

Ganglionectomy combined with periarterial sympathectomy of the subclavian artery gave complete relief of pain in seven cases of moderately severe and severe causalgia of the upper extremity. In the long-standing cases of causalgia, even though the pain was relieved, the functional results were poor due to the secondary fibrotic changes in the soft tissues of the hand.

Early radical sympathectomy in ten cases prevented the development of contractures and other secondary changes.

Early reparative surgery, within three weeks of the initial injury, followed by one or two paravertebral injections of procaine, was used in four cases. Relief of pain was achieved and secondary contractures were prevented.

Early relief of pain is essential in order to prevent the development of soft tissue changes. This relief can best be obtained by early reparative surgery followed, when necessary, by paravertebral injections of procaine.

Radical sympathectomy should be reserved for those patients in whom it is impossible to obtain clean healing of the wounds which involve the nerves or in whom the pain persists. Sympathectomy should be performed early, before the development of fibrosis and contractures.

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VARIATIONS IN THE SYNDROME OF THE RUPTURED INTERVERTEBRAL DISC IN THE LUMBAR REGION

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THE syndrome of simple rupture or protrusion of the intervertebral disc has been defined very clearly in recent years, providing much clarification of the problem of low back pain. The syndrome has been recognized with increasing frequency, particularly since Mixter's publications, and today it is of major neurosurgical consideration. Approximately 80 per cent of ruptured lumbar discs elicit a classical picture, but the remaining 20 per cent present puzzling and complex variations which demand the most detailed and careful study for differential diagnosis. The site of rupture (whether lateral or transverse in relation to the spinal canal), the direction of the protrusion of the disc, and other sequelae determine the resulting symptoms and signs. The present paper is concerned with a discussion of the variations in the syndrome in relation to the anatomic changes with which they are associated.

Simple rupture or protrusion of the disc to impinge on a single spinal nerve root, as shown in Fig. 1, *A*, results in symptoms and signs which are relatively few and uniform. The classical picture associated with this condition may be described as follows: The subjective changes presented by patients with laterally protruding ruptured discs, as well as the objective ones found on examination, are fairly characteristic and vary mostly in intensity according to the stage of advancement. A history of trauma, single or repeated, can be obtained from the majority of these patients; the remainder of the individuals, with a few exceptions, have had a sudden onset of pain even if no history of trauma is obtainable. The pain is confined to the lumbosacral region for a variable length of time or until the protrusion of the disc takes place and the root compression is established, which results in complaints of radiating pain in the posterior aspect of one of the lower limbs. These radicular pains are variable in extent but are always influenced by motion in the lumbosacral spine and by changes in the intraspinal pressure resulting from the variability of congestion in the rachidian veins, brought on by increased abdominal and thoracic pressure, as during coughing, sneezing, and straining. The radicular pain, at times, may have localizing value, but this depends largely upon the patient's ability to observe the distribution of the radiation.

Radicular pain is frequently accompanied by paresthesiae, which are confined at times within the limits of the distribution of pain but more often within an area distal to that inside the range of pain. Other patients complain of mere numbness, which, also, is felt beyond the painful area. Thus, it is rather common for patients to complain of excruciating pain in the posterior

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thigh and calf and, simultaneously, of numbness in the big toe or the little and fourth toes. Few will feel pain down to the toes, though such a complaint is encountered occasionally.

The objective changes found after protrusion of the disc may be classified as follows: (1) changes characteristic of a ruptured lumbar disc and (2) changes that have localizing value with respect to the particular nerve roots compressed. The former changes are mechanical and defensive and are due to bodily responses induced to guard against the shocking pain, for example, the paravertebral muscle spasm, abnormal posture of the spine, limitation of straight leg raising, presence of Lasèque's sign. The localizing changes are neuropathologic in nature and, therefore, of much graver significance. Such changes are, briefly, the early selective weakness and hypotonia, followed by

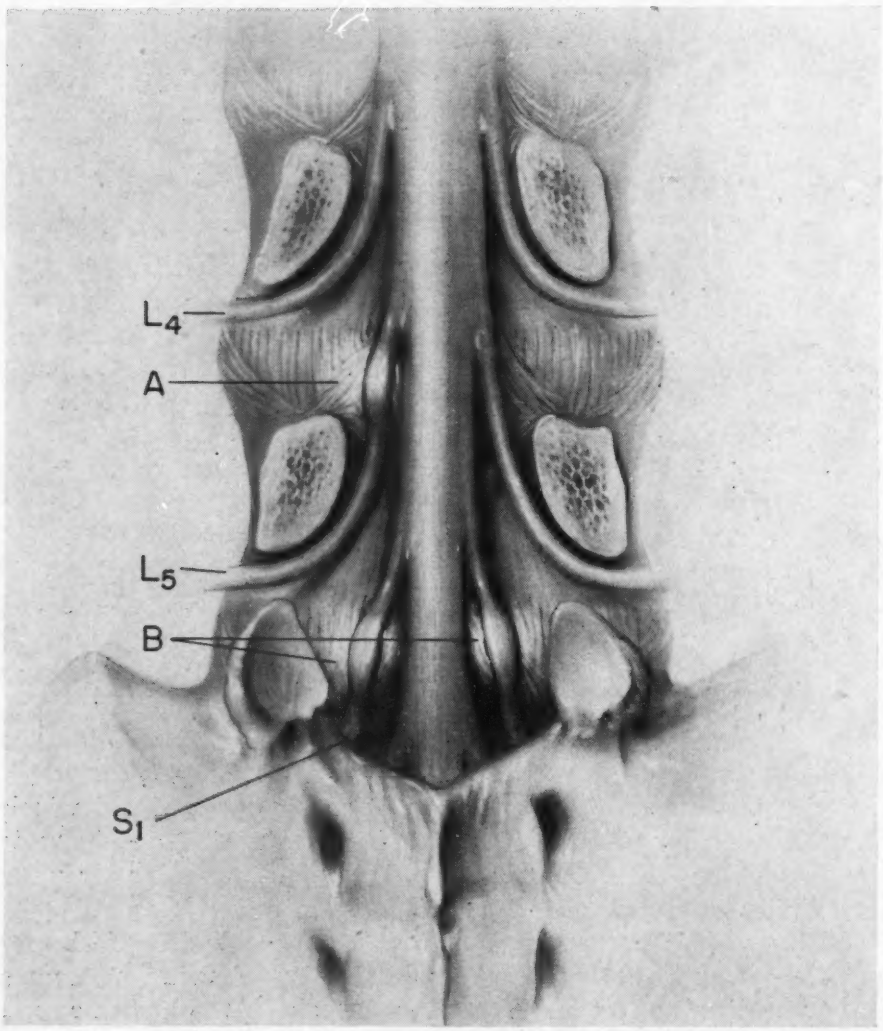

Fig. 1.—*A*, Simple lateral protrusion at the fourth lumbar interspace with compression of the fifth lumbar root. *B*, Bilateral protrusion at the fifth lumbar interspace with compression of the first sacral root on both sides. *A* and *B*, Multiple protrusions with compression of roots L_5 left, S_1 right, and S_1 left.

atrophy of certain muscle groups, sensory impairment in certain dermatomes, and, finally, changes in the tendon reflexes of the lower limbs.

On the basis of these findings, a ruptured intervertebral disc at the fourth lumbar interspace can be recognized easily when it protrudes laterally. The mechanical defensive signs are present; the patient complains of sciatic pain and numbness of the big toe; and the examiner finds weakness of the anterior tibial and peroneal muscle groups, decreased knee jerk, and sensory impairment over the anterior aspect of the leg and dorsum of the foot. Likewise, rupture at the fifth lumbar interspace and compression of the first sacral root can be diagnosed when the patient complains of numbness in the two lateral toes along with sciatic pain and when examination reveals drooping of the gluteal fold, decrease or absence of ankle jerk, and impairment of sensation over the lateral aspect of the leg and foot.

In contrast with this clearly defined clinical syndrome are the variations in the symptoms and signs associated with other types of rupture of the intervertebral discs or complications and progressive changes in the simple type. Correlation of clinical with operative findings has revealed a number of conditions responsible for variations in the syndrome; these are:

1. The rupture has taken place higher than the fourth lumbar interspace.
2. Lateral protrusion has not occurred, or the protrusion is large enough to affect more than one or two nerve roots.
3. The protrusion has been bilateral.
4. Two or more adjacent discs have ruptured.
5. The main bulk of the ruptured disc is no longer attached to its interspace but has wandered into the spinal canal.
6. The protrusion is so massive that it completely blocks the spinal canal and thus produces the syndrome of cauda equina.

First, ruptures at the higher interspaces cause complaints mostly of back pain or flank pain and the helpful sciatic distribution is missing, as are many of the other easily detected signs of rupture of the lower discs. The following case history, briefly summarized, may serve as an illustration.

CASE 1 (History No. 76477).—A 39-year-old man experienced onset of pain in the right lumbar region ten weeks before admission. There was no radicular pain but pain aggravated by motion in lumbosacral spine and by increased intraspinal pressure. Abnormal objective findings were: paravertebral muscle spasm in right lumbodorsal region, with tenderness on pressure in this area. In this case there was no scoliosis, no limitation of forward bending, no limitation of straight leg raising, no tenderness of sciatic nerves, no motor weakness, and no sensory impairment. Lasèque's sign was negative bilaterally. Tendon reflexes were active and equal in the lower limbs. Fluoroscopy was carried out after intraspinal injection of lipiodol and a large filling defect was encountered at the first lumbar interspace on the right side. Operation revealed a ruptured disc in this space, seen intradurally as a protrusion occupying the right half of the spinal canal and displacing the cauda equina posteriorly.

Second, when the ruptured disc fails to protrude laterally (Fig. 2) or if it is sufficiently large (Fig. 3), it may compress several roots and may even affect all of the roots that have not left the spinal canal by their respective interver-

tebral foramina. This syndrome may begin with inconspicuous complaints of low back pain that may suddenly progress into the well-established picture of a cauda equina tumor, or it may acquire the character of a single-root compression for a variable length of time, and it may become bilateral in character.

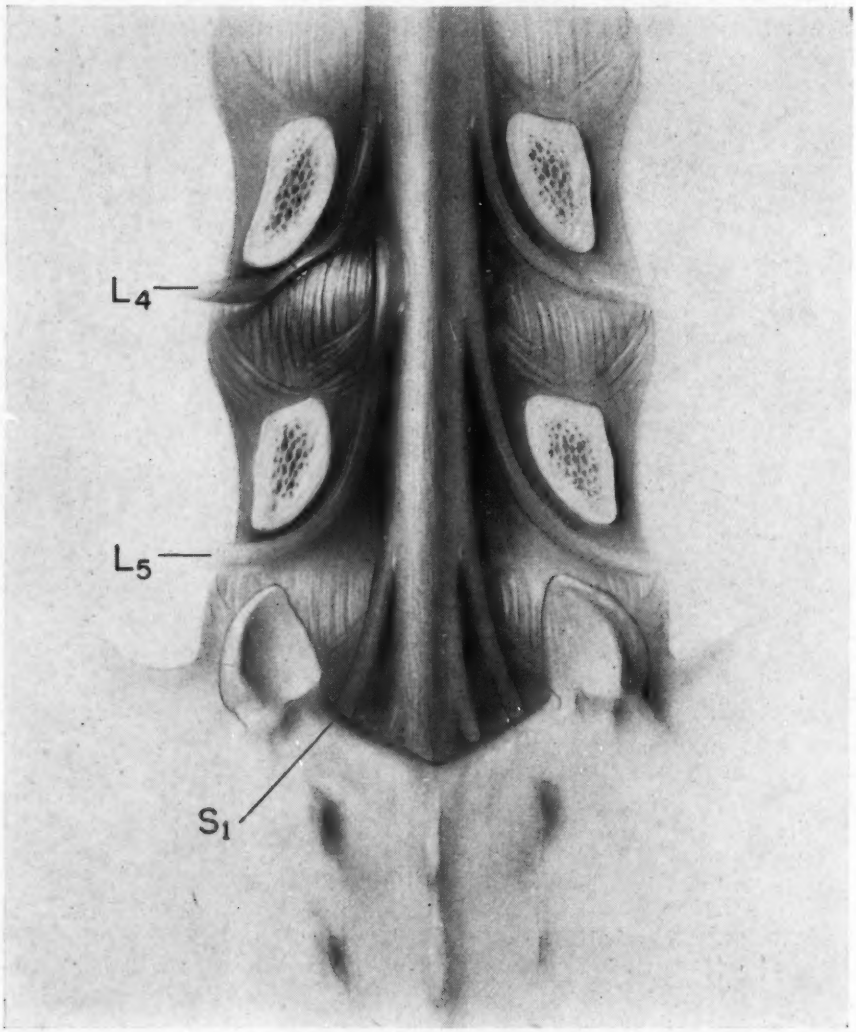

Fig. 2.—Lateral protrusion at the fourth lumbar interspace with compression of the adjacent fifth lumbar and first sacral roots.

The complaint of a patient so affected will naturally differ from those caused by a steady, solid unilateral compression, and it is particularly the changeability of symptoms that is important here. In such cases the complaints are often uninformative, and the defensive mechanical signs are quite different, not being nearly so outspoken. The neuropathologic signs are often vague and late in developing, according to the extent of compression in the one case and the number of roots affected in the other. Only the subjective symptoms may be manifest for a long time before the compression reaches a

degree such as to produce objective changes. The following cases will serve as illustrations.

CASE 2 (History No. A94392).—A 47-year-old man experienced gradual onset of low back pain three years prior to admission. Severe exacerbation of low back pain associated with bilateral hip pain radiating down the posterior thighs to the knees was present during a few months prior to admission. Abnormal objective findings were: diminished lordosis and an almost complete rigidity of the lumbar spine, forward bending limited to 45 degrees, marked bilateral paravertebral lumbar muscle spasm, tenderness to palpation in the lumbosacral area, straight leg raising limited to 45 degrees bilaterally, and Lasègue's sign positive bilaterally. In this case there was no tenderness of the sciatic nerves, no muscle weakness, and no sensory impairment. Tendon reflexes in the lower limbs were: knee jerks ++ right, +++ left; ankle jerks + right, ++ left. Fluoroscopy, carried out after intraspinal injection

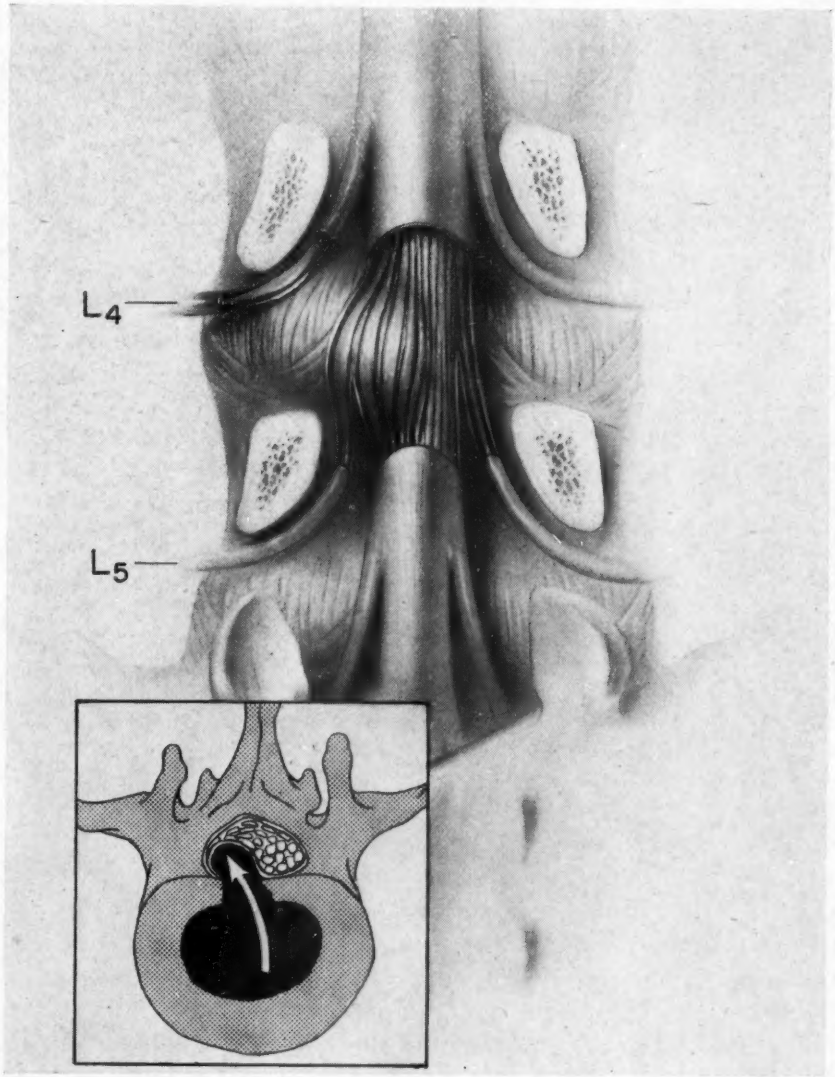

Fig. 3.—Large medial protrusion at the fourth lumbar interspace with multiple root compressions.

of lipiodol, showed a large filling defect at the fourth lumbar interspace. Operation revealed a ruptured disc at this level, the protrusion extending across the entire space, primarily on the right side. The protrusion was also displaced upward over the body of the fourth lumbar vertebra.

CASE 3 (History No. B42091).—A 45-year-old man had gradual onset of low back pain two years before admission. There was radiation of pain to the left hip and down the posterior left thigh ten months before admission. Five months later severe exacerbation of low back pain with radiation to both posterior thighs, more marked on the left side, was present, with range down to the calf and associated with numb feeling in both feet. There were no bladder or bowel disturbances. Pain increased by motion in the lumbosacral spine and on increased intraspinal pressure. Abnormal objective findings were: moderate tenderness on palpation of lumbosacral area, forward bending limited to 45 degrees by low back and bilateral hip pain. In this case there was no scoliosis, no paravertebral muscle spasm, straight leg raising unlimited bilaterally, Lasègue's sign negative bilaterally, no motor weakness, and no sensory impairment. Tendon reflexes in the lower limbs showed minimally decreased left knee jerk; the ankle jerks were active and equal. Fluoroscopy after intraspinal injection of lipiodol showed an almost complete block at the third lumbar interspace. Operation revealed a ruptured disc at this level, protruding 1 cm. backwards into the spinal canal.

A third variation of the rupture (Fig. 1*B*) is the bilaterally protruding disc, in which condition bilateral sciatica is the main complaint and the usual signs of a single-root compression are present on both sides. However, the difference between the second variety and this one is frequently slight and fleeting, at times a matter only of degree. The following case may illustrate this.

CASE 4 (History No. B23163).—A 39-year-old woman experienced sudden onset of severe pain in the right hip without any obvious cause thirteen months prior to admission; she was in the eighth month of pregnancy. Right sciatic pain soon developed, ranging down to the heel, together with low back pain. Six weeks prior to admission severe exacerbation of low back pain associated with bilateral sciatic pain and numbness in both feet was present. Abnormal objective findings were: marked tenderness on palpation over lumbosacral area, lumbodorsal scoliosis with convexity to the left, marked tenderness of both sciatic nerves, and moderate, nonselective weakness of the lower limbs, more marked on the right side. Straight leg raising was limited to 45 degrees bilaterally, and there was sensory impairment over the lateral aspect of the leg and foot from the knee down bilaterally. Tendon reflexes in the lower limbs were: knee jerks + + bilaterally; ankle jerks 0 right, + left. Operation revealed a ruptured disc at the fifth lumbar interspace protruding laterally on both sides, with complete rupture on the right side.

The fourth variation, which may render the diagnosis difficult and in some respects even mislead in the detection of a ruptured intervertebral lumbar disc in the usual conception of that syndrome, is seen when multiple ruptures (Fig. 1, *A* and *B*) have occurred and the protrusions necessarily compress more than one nerve root. The multiple ruptures may be either unilateral or bilateral. It is to be noted that one disc protruding laterally may impinge, at times, on two adjacent roots. This, however, does not cause much confusion, as the signs from one of the roots usually predominate over those from the other root under compression. The following case illustrates clearly how extensive the lesion may be and, therefore, how complicated are the resulting signs.

CASE 5 (History No. 22719).—A 59-year-old white man had a history of repeated attacks of low back pain of twenty-five years' duration. He had had attacks of sciatica on the left side during a period of seven years. The pain in the present attack of sciatica originated in the left hip and radiated down the anterior aspect of the thigh to one knee Pain was aggravated by increased intraspinal pressure and motion in lumbosacral spine. Abnormal objective findings were: marked tenderness on palpation in the lumbosacral area, straight leg raising unlimited on right side and 45 degrees on left, and Lasègue's sign positive on left. There was marked atrophy of the left anterior tibial and peroneal muscle groups, hypotonia of all muscle groups, and marked generalized weakness of the entire left lower limb, with an almost complete foot drop. There was sensory impairment over the anterior aspect of the left thigh and leg down to ankle. The knee jerks were absent bilaterally; ankle jerks were + on right, 0 on left. In this case there was no scoliosis, no paravertebral spasm, but moderate stiffness of the lumbar spine. After intraspinal injection of lipiodol, fluoroscopy showed irregular defects at the second, third, and fourth lumbar interspaces. Operation revealed an extremely large transversely protruding disc obliterating completely the subarachnoid space at the second lumbar interspace, a laterally protruding disc at the third lumbar interspace on the right side, and a laterally protruding ruptured disc at the fourth lumbar interspace on the left side.

A fifth variety arises when a large portion of the ruptured disc becomes detached and escapes from its interspace, as seen in Fig. 4. These discs may wander and settle somewhere within the spinal canal or in the extradural space, and they have been found even posterior to the cauda equina. Naturally, the complaints and signs will change from time to time in such a case, as this syndrome usually will begin as that of an ordinary lateral protrusion and then later deviate from the pattern when the disc wanders and more than one root becomes involved. The following short case history may show this grossly.

CASE 6 (History No. B77241).—A 41-year-old man, in 1936, experienced sudden onset of severe pain in the low back, radiating into the calf of the right leg. A body cast was applied and worn for twenty-three weeks, during which period the pain slowly diminished and finally disappeared. The patient was asymptomatic then until 1940, when the right sciatic pain recurred after heavy lifting, this time associated with weakness of the right foot. Pain disappeared in one week and the weakness of the right foot diminished gradually. In December, 1945, or one month prior to admission, the patient again strained his back and experienced an immediate onset of pain in that region, this time radiating into the left calf and occasionally into the right. One week later foot drop on the left was observed. Pain was aggravated by increased intraspinal pressure and motion in the lumbosacral spine. After admission, the sciatic pain on the left side disappeared but reappeared and became confined to the right side. Positive pathologic findings were: lumbodorsal scoliosis, convex over to the right; bilateral paravertebral lumbar muscle spasm; forward bending limited to 15 degrees; tenderness on palpation over the lumbosacral area; tenderness of the right sciatic nerve; straight leg raising 75 degrees on the left, 65 on the right; Lasègue's sign negative bilaterally, complete foot drop on the left; marked weakness of dorsiflexion of the foot on the right; and sensory impairment over the lateral aspect of both legs and feet below the knee. Reflexes were: knee jerks ++ right, + left; ankle jerks 0 right ± left. At operation, this patient was found to have a markedly narrowed fourth lumbar interspace. The disc had ruptured through the posterior longitudinal ligament and was lying free as a loose fragment in the extradural space over the posterior lateral surface of the dura, and another fragment was present lateral to the nerve root and dura.

Sixth, when the protrusion is exceptionally large, extending across the entire space (Fig. 5), most commonly encountered at the fourth and fifth lumbar

interspaces, it produces a more or less complete block of the spinal canal and thus compression of the entire cauda equina. . The picture simulates that of a cauda equina tumor; that is, the bladder and bowel disturbances along with sexual impotency predominate in the presence of saddle anesthesia and weakness of the lower limbs. The history in these cases is particularly important

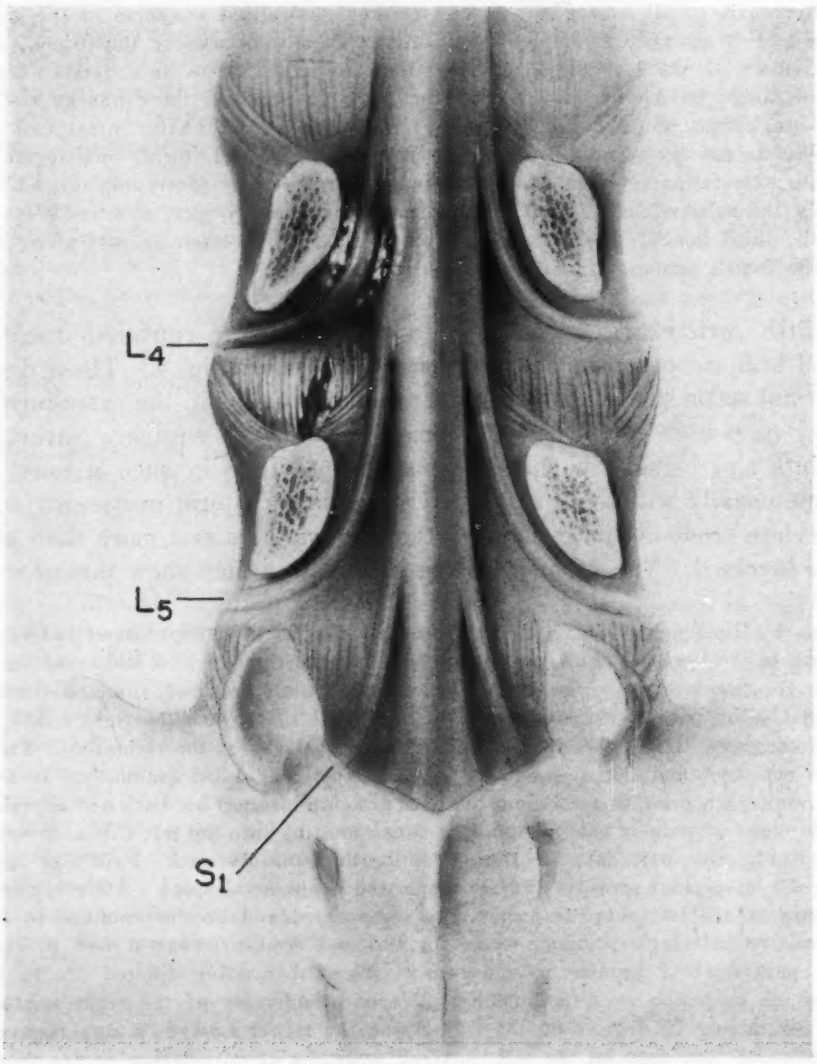

Fig. 4.—Wandering disc. Rupture occurred at the fourth lumbar interspace where the tear is seen, and the displaced disc fragment is seen over the posterior surface of the body of the fourth lumbar vertebra compressing the fourth lumbar root.

because if there is a background of trauma, or if the history reveals a sudden onset of pain and sudden development of the neuropathologic signs, the assumption is well justified that a ruptured disc, and not a tumor, is responsible for the disability. If this is recognized early, the changes of recovery are so much the greater.

CASE 7 (History No. B40164).—A 66-year-old man had sudden onset of low back pain and left sciatic pain nine months prior to admission. At the same time, there was moderate pain in the posterior aspect of the right lower limb, coming on after heavy lifting. A few days later there were urinary incontinence, weakness in both lower limbs, and marked constipation. The patient was confined to bed for nine months, during which time there was complete impotentia coeundi. Abnormal findings were: patient unable to stand without crutches, marked tenderness on palpation of lumbosacral area, both sciatic nerves tender, straight leg raising limited to 20 degrees on left and 30 on right, and Lasègue's sign positive bilaterally. There were marked weakness and atrophy of both the dorsiflexors and the plantar flexors bilaterally, more marked on the left side. Both gluteal folds were atrophic and toneless. Sensory examination revealed a saddle anesthesia extending down the posterior thighs and leg on both sides, including the lateral aspect of feet and the fourth and fifth toes. Tendon reflexes were: knee jerks ++++ right, +++ left; ankle jerks absent bilaterally;

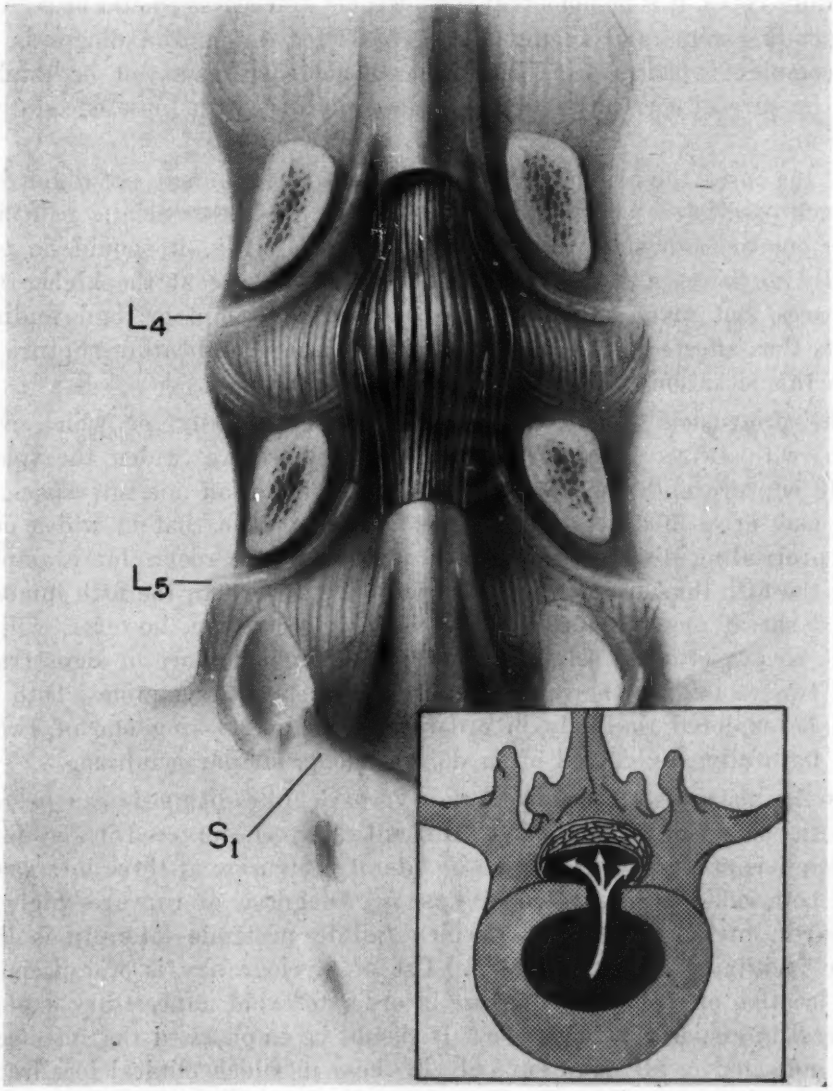

Fig. 5.—Massive transverse protrusion at the fourth lumbar interspace with compression of the entire cauda equina.

plantar reflexes down. Fluoroscopy, after intraspinal injection of lipiodol, revealed a large defect in the lipiodol shadow overlying the fourth and fifth interspaces. Operation disclosed a ruptured disc at the fifth lumbar interspace, with the largest protrusion in the midline but extending out to both sides. The disc at the fourth interspace also was ruptured and protruded laterally toward the right side.

COMMENT AND CONCLUSION

The observations described in the present paper reveal a number of variations that occur in the rupture of the intervertebral disc and in the resulting associated syndromes. While much interest has been shown in differential diagnosis of the simple ruptured disc, less attention has been given to the detection and recognition of the more complicated or progressive types of the condition. From a consideration of the differences in the pathologic anatomy of the various types, it is obvious that considerable differences should be seen in the corresponding signs and symptoms. A basis for differential diagnosis of the more complex ruptures from other neurologic conditions can be established chiefly by careful correlation of the clinical findings with those encountered at operation.

At the onset, the histories of the individual varieties may not differ greatly. Low back pain is the outstanding complaint in all cases. Sciatic pain may be felt on one or both sides or not at all. Theoretically, it should be possible clinically to detect a simple ruptured, protruding disc at the higher lumbar interspaces, but many other ailments induce the symptoms and findings of patients thus affected. A symptom of much value in indicating rupture of the disc in this situation is the complaint of radicular pain.

The protrusion that occurs otherwise than laterally, or which is large enough, will always affect several roots and, therefore, widen the sphere of possible rupture and compression to that of more than one interspace. Confusion may arise in differentiating this condition from that in which one laterally protruding disc compresses two adjacent nerve roots; for example, the disc at the fifth lumbar interspace may impinge upon both the fifth lumbar and the first sacral roots simultaneously. Such a protrusion, however, will cause a fairly clear picture of sciatica, usually with predominance of signs from one of the two roots. In the presence of such signs and symptoms, both spaces should be explored routinely in order to avoid overlooking one of two discs which, naturally, could, and often do, produce a similar syndrome.

In the instances of certain of the types, definite diagnosis can be reached only with the aid of myelography. Difficulties are encountered in the diagnosis of multiple ruptures; for example, the lateral protrusion at three interspaces on one or both sides, as illustrated by Case 5. Diagnosis of ruptures higher than the fourth interspace and those which fail to protrude laterally is likewise greatly facilitated by myelography. Use of myelography is of especial value in the location of the wandering disc in order to avoid unnecessary exploration of several interspaces at operation. It should be emphasized that myelography is not indicated in all cases but only in those in which clinical localization of the rupture is not possible. In all apparently clear cases of lateral protrusions

at the fourth or fifth lumbar interspace, exploration of both interspaces is the rule. In such cases continued complaint of pain is considered an indication for myelography in order to avoid missing multiple discs.

The massive protrusions that obliterate the spinal canal exert pressure on all roots that have not left the canal. These are encountered most frequently at the fourth and fifth lumbar interspaces. These conditions are associated with the three most discouraging signs of nervous diseases, namely, loss of urinary and fecal control along with sexual impotency. Unfortunately these signs are frequently accompanied by incurable conditions. A careful consideration of the history, however, will simplify differentiation, since it is well known now that a ruptured disc often is responsible for paraparesis associated with urinary and fecal incontinence and loss of sexual potency. Whether these neuropathologic signs are reversible or not depends upon their duration.

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A MODIFICATION OF THE ROUX TECHNIQUE FOR ANTETHORACIC ESOPHAGEAL RECONSTRUCTION

ANASTOMOSIS OF THE MESENTERIC AND INTERNAL MAMMARY BLOOD VESSELS

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ONE of the most satisfactory methods of esophageal reconstruction thus far developed is that originally described by Roux[1] in 1907. In this method the intestine is divided a short distance from the ligament of Treitz, and a long segment of jejunum is mobilized by severing the first three or four primary mesenteric vessels, the circulation of the mobilized loop being maintained through the arcuate vessels which run parallel with the intestine. The mobilized loop of jejunum is placed beneath the skin of the anterior chest wall, the upper end is anastomosed to the proximal esophagus, and the continuity of the intestinal tract is restored in the abdomen by an end-to-side anastomosis distal to the mobilized loop. Yudin[2] reported eleven successful cases completed by this method.* He stressed, however, the importance of the variations of the vascular pattern in the jejunal mesentery and stated that at times the size or arrangement of the vessels may be such as to preclude the performance of this type of reconstruction. Ochsner and Owens[3] reviewed the literature up to 1934 and found that gangrene of the jejunal loop developed in 22 per cent of the reported cases.

This paper reports a method of anastomosing one of the primary vessels in the mesentery of the mobilized loop to the internal mammary vessels, thereby reducing the hazard of necrosis of the jejunal loop due to insufficient circulation and overcoming some of the difficulties encountered in cases with an unfavorable mesenteric vascular pattern. The size of the vessels to be anastomosed makes the procedure unsuitable for infants or small children.

TECHNIQUE

The abdomen is entered through a left upper rectus or midline incision and the first portion of the jejunum is identified at a point 8 to 10 cm. from the ligament of Treitz. The intestine and the arcuate vessels are divided. The size and position of the first five primary mesenteric vessels are inspected. To free sufficient jejunum to reach above the clavicle it is usually necessary to divide four of the primary mesenteric vessels although this detail must be determined for each case (Fig. 1). Two primary mesenteric arteries and veins can be divided with impunity. Before the third and fourth sets are divided, however, they should be occluded with a bulldog clamp and the circulation of the

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*The editor of the journal in which his paper appeared credits him with twenty-one completed cases by this method at the time of publication.

terminal portion of the loop evaluated. If the blood supply is dubious the clamp should be left on for five to ten minutes as the circulation frequently improves during this period. The presence or absence of pulsation in the smaller mesenteric vessels and the color and peristaltic activity of the intestine are the criteria to be followed in testing the adequacy of the circulation. If a sufficient length of jejunum with adequate circulation is obtained in this manner, obviously no further procedures are necessary other than care to prevent obstruc-

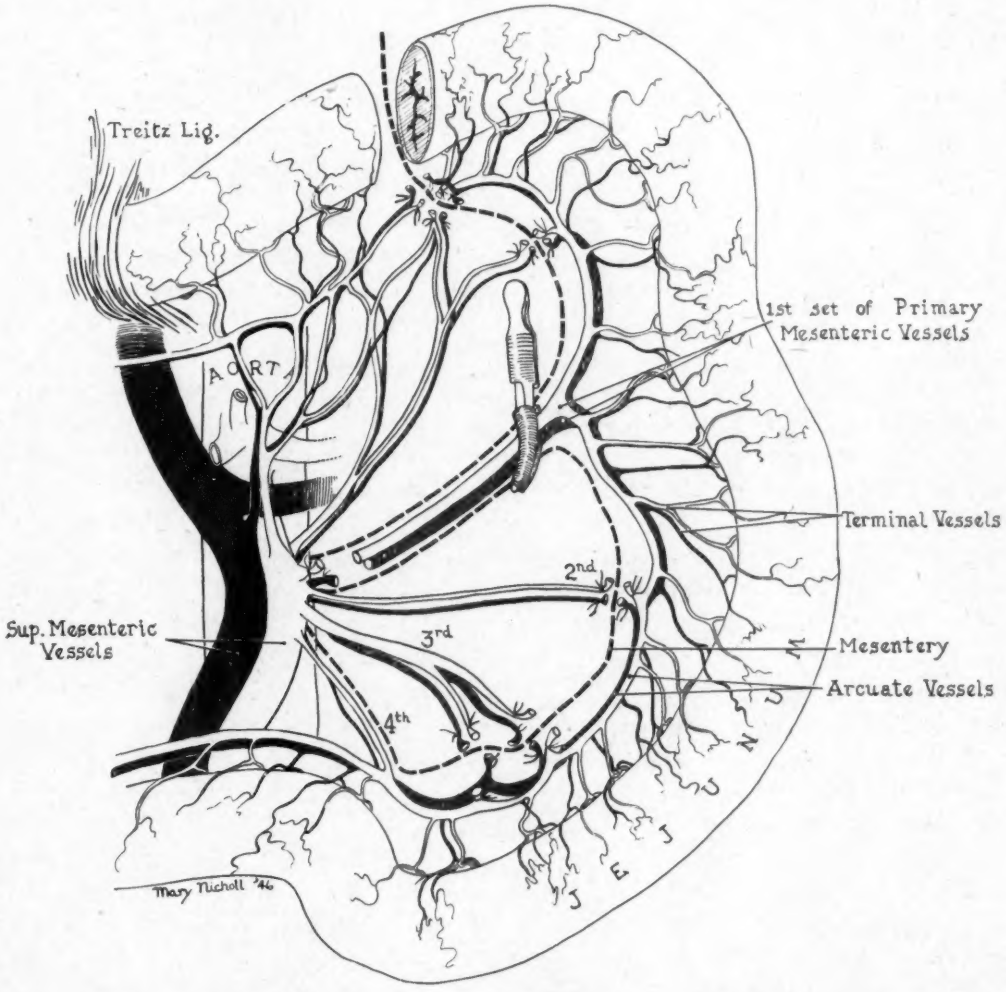

Fig. 1.—Division of jejunum and mesenteric vessels with bulldog clamp occluding first set of primary mesenteric vessels; arcuate vessels unobstructed throughout length of jejunal loop.

tion of the vessels by twisting when the jejunum is placed over the costal margin and beneath the skin of the chest wall. If, however, the arteries and veins to be divided are large, well-developed vessels, the vessels distal to this point are usually smaller and are inadequate to provide the circulation for the mobilized loop. It is this type of vascular arrangement in which anastomosis of the mesenteric and mammary blood vessels is indicated.

The first or second pair of primary mesenteric vessels is clamped with bull-dog clamps, the proximal ends are ligated near the superior mesenteric vessels, and the vessels are divided. It is then necessary to decide at what point these vessels should be anastomosed to the internal mammary vessels to allow the jejunal loop to extend to the desired level in the neck. At the selected site a longitudinal incision is made along the left border of the sternum and two costal cartilages are resected. The internal mammary vessels are exposed and

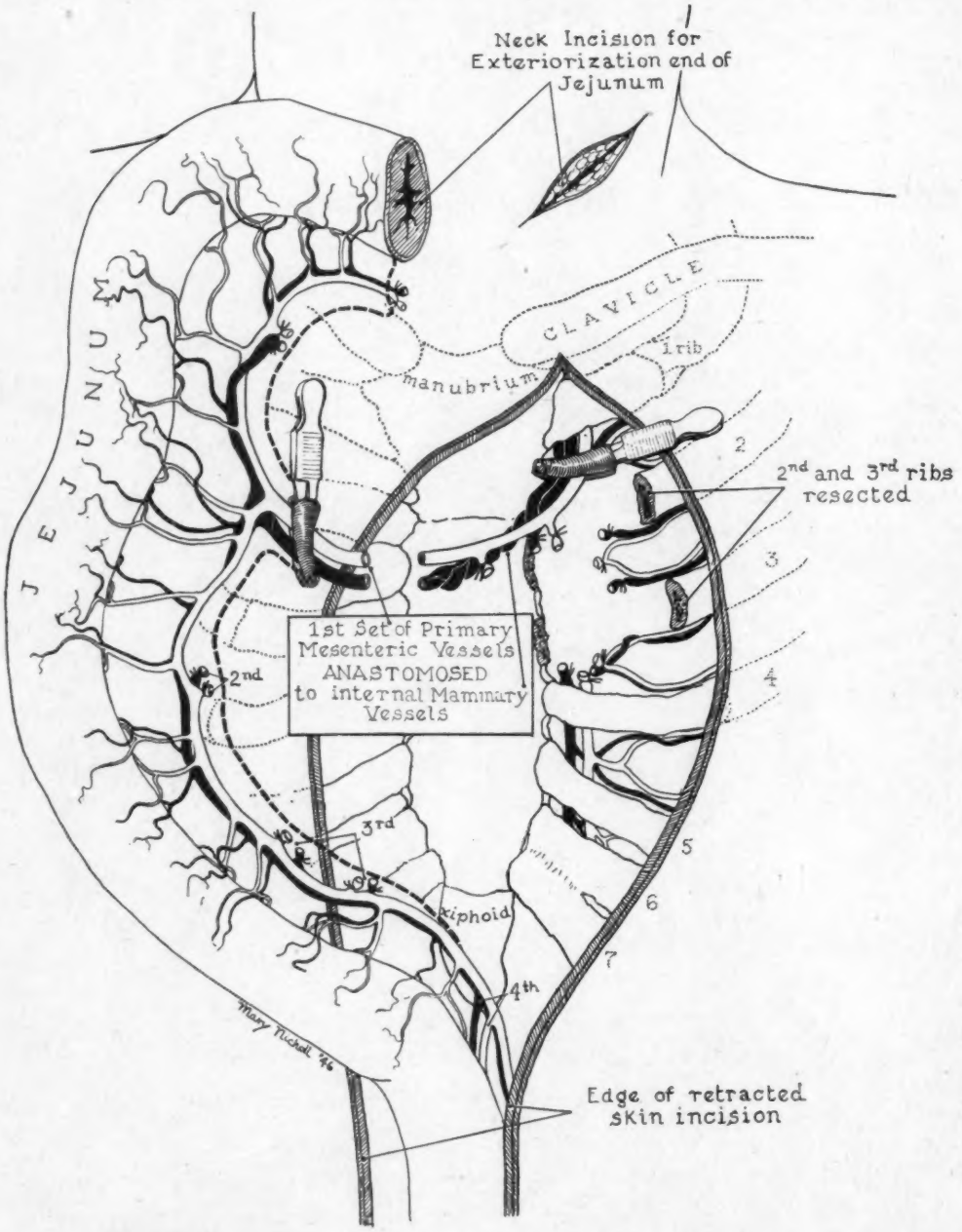

Fig. 2.—Jejunal loop advanced onto thorax; second and third costal cartilages resected and internal mammary vessels prepared for anastomosis to primary mesenteric vessels.

ligated at the lower angle of the incision, and the upper ends are clamped with bulldog clamps. An end-to-end anastomosis is performed between the arteries and veins with a continuous 00000 silk suture (Fig. 2). A Beebe binocular loupe magnifying lens aids in this portion of the procedure. After the anastomosis is completed it is possible to divide additional mesenteric vessels if greater length of the loop is needed. A subcutaneous channel is made over the anterior chest wall and the end of the intestinal loop is brought to the outside through the skin of the neck along the anterior border of the left sternomastoid muscle. The continuity of the intestinal tract is restored by an end-to-side anastomosis between the proximal end of the jejunum and the side of the jejunum distal to the mobilized loop. At a subsequent operation the cervical esophagus is mobilized as previously described,[4] and at the third operation the esophagojejunal anastomosis is completed.

CASE REPORT

W. C., a 28-year-old colored man, was admitted to the Johns Hopkins Hospital on April 5, 1946, because he was unable to retain food or liquids.

In October, 1943, he swallowed lye, and shortly thereafter a severe stricture of the esophagus developed. From January, 1944, until October, 1945, he had received weekly esophageal dilations at another hospital but had been able to swallow and retain only liquids. After the dilations were discontinued he began to vomit more frequently and this difficulty steadily increased up until the time of admission. He had lost thirty pounds and was severely dehydrated. X-ray examination of the esophagus and esophagoscopy demonstrated an impermeable benign stricture in the middle third of the esophagus.

On April 15, 1946, the first stage of an antethoracic esophageal reconstruction was performed. Through an upper midline incision the first portion of the jejunum and the arcuate vessels were divided about 10 cm. from the ligament of Treitz. The first and third primary mesenteric arteries and veins were fairly large, and the third vessels branched about one-third of the way from the root of the mesentery. The second, fourth, and fifth vessels were small and poorly developed. Distal to this region the branching of the mesenteric vessels made them unsuitable for extensive mobilization of the intestine. With the use of methods previously described an adequate length of viable jejunum could not have been mobilized, and it was decided to anastomose the first set of primary mesenteric vessels to the internal mammary vessels as described in the foregoing sections.

Immediately upon release of the bulldog clamps, pulsations which had previously been absent were seen in the small terminal intestinal arteries at the end of the intestinal loop, and the appearance of this portion of the loop, which had become cyanotic, returned to normal. The hyperactive peristalsis of the loop ceased and the bowel responded with normal peristaltic contractions to mechanical stimulation.

After testing with temporary occlusion, the second branch of the third primary mesenteric artery was divided without affecting the circulation in the terminal portion of the jejunal loop. This step permitted the end of intestine to be brought to the outside through an opening in the left lower cervical region. The loop entered the abdomen through the upper portion of the midline incision. The continuity of the intestinal tract was restored.

At the second operation twelve days later the cervical esophagus was mobilized and placed subcutaneously as previously described.[4] After operation an esophageal fistula developed through this incision, either from trauma at the time of operation or as a result of pressure necrosis at the site of the "muscular sling" which held the esophagus anteriorly (Fig. 3). This mishap delayed the third operation until thirty-three days later.

It had been planned to anastomose the end of the jejunal loop to the side of the esophagus, but the development of the esophageal fistula, which arose on the posterior surface of the esophagus, necessitated division of the esophagus, closure of the aboral end, and performance of an end-to-end anastomosis between the jejunal loop and the oral end of the esophagus. This junction was made with two rows of interrupted chromic catgut sutures. The anastomosis, which was at the level of the thyroid cartilage, healed uneventfully. Two weeks after operation the patient was given liquids by mouth. A few days later he was permitted to take solid foods, the first he had swallowed and retained in two and one-half years. Following this he was able to eat all varieties of foods. The passage of food through the intestinal loop was slower than normal but was unobstructed (Fig. 4).

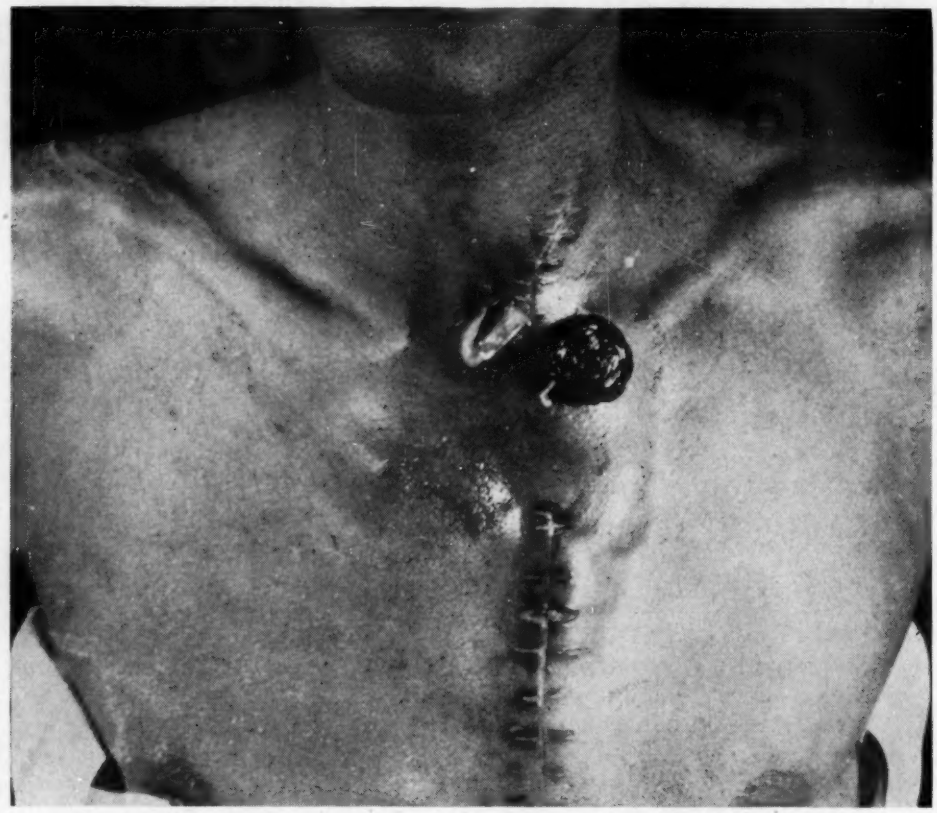

Fig. 3.—Upper end of jejunal loop exteriorized above left clavicle; neck incision for mobilization of cervical esophagus.

SUMMARY

The Roux procedure for antethoracic esophageal reconstruction has the great advantage over other methods of esophageal repair of accomplishment in two or three stages. Yudin has reported cases completed in a single operation although he recommended that the operation usually be divided into two stages. The procedure provided a tube lined with mucous membrane with a single esophageal anastomosis and an intraperitoneal end-to-side intestinal anastomosis. Except in the very high pharyngeal strictures, it obviates the need for any type of skin tube and the precarious skin-mucous membrane anastomosis.

The chief disadvantage of the method has been the frequent inability to obtain a sufficient length of viable jejunum to reach above the level of the esophageal obstruction. This difficulty is largely due to normal variations in the mesenteric vascular pattern to the proximal jejunum. Excessive fat in the mesentery may also interfere. Yudin has amply demonstrated that when the vascular arrangement is favorable a sufficient length of jejunum can be obtained to reach to the mastoid region. The percentage of cases in which an unfavorable

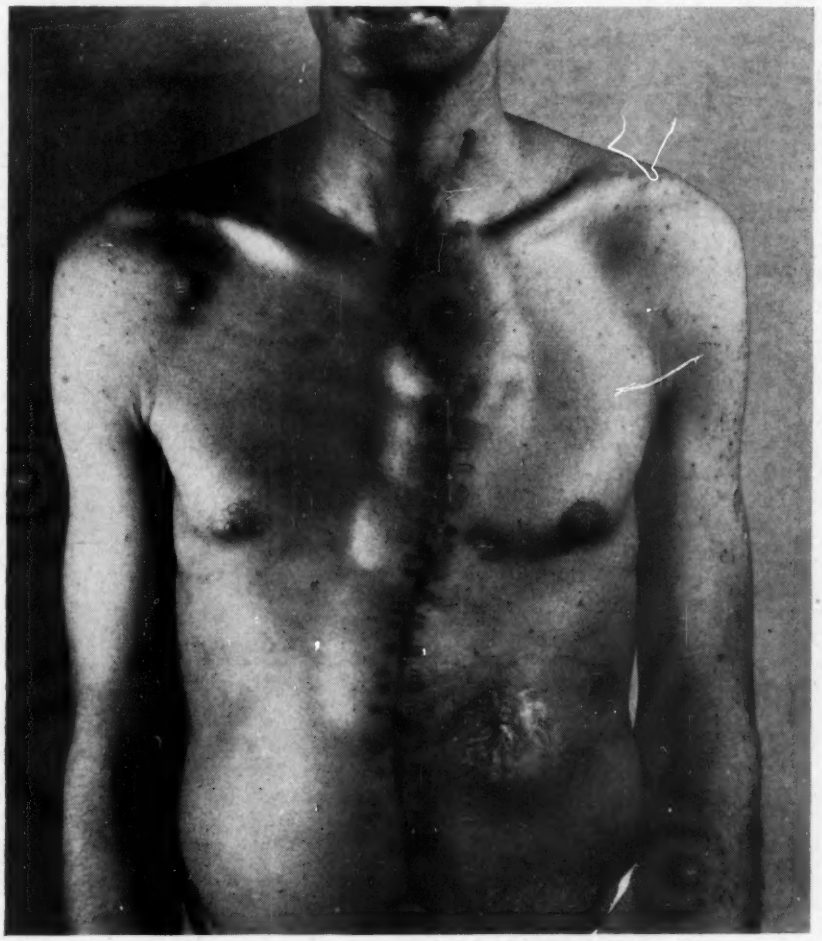

Fig. 4.—Patient two and one-half months after completion of antethoracic esophagus; incisions all well healed and patient has gained fifteen pounds.

vascular pattern is encountered is unknown; Ochsner and Owens' report to 1934 of the occurrence of gangrene in 22 per cent of the reported cases in which this method was attempted suggests that it may be high. It is in this group of patients that one of the first two sets of primary mesenteric vessels is apt to be large. The modification of the procedure suggested in this paper utilized these well-developed vessels for a blood vessel anastomosis to preserve to some extent the circulation of the jejunal loop.

It has not been possible to demonstrate directly the patency of this blood vessel anastomosis after the conclusion of this type of operation, but it is believed that if the anastomosis remains patent for a matter of four or five days, the circulation of the mobilized loop will have adjusted itself through the longitudinal arcuate vessels. After a period of two or three weeks, collateral circulation through the subcutaneous tissue should be sufficient to maintain the intestine, as was previously demonstrated by Longmire and Ravitch.[4]

CONCLUSIONS

1. The Roux type of antethoracic esophageal reconstruction is one of the most satisfactory methods of esophageal repair.

2. Unfavorable arrangement of the primary mesenteric vessels to the first portion of the jejunum may at times make it impossible to obtain a sufficient length of intestine to reach above the level of the esophageal obstruction.

3. In certain cases where the mesenteric vascular pattern is unfavorable, anastomosis of one of the primary mesenteric arteries and veins to the internal mammary artery and vein will ensure an adequate blood supply to the mobilized intestine.

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THE USE OF TESTOSTERONE PROPIONATE IN THE TREATMENT OF ADVANCED CARCINOMA OF THE BREAST

II. The Treatment of Osseous Metastases

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IN A preliminary communication the effects of large doses of testosterone propionate on advanced carcinoma of the female breast were described. The results obtained in twelve patients who received this therapy, nine with widespread soft part disease and three with osseous metastases, were reported at the end of six months of treatment. In the present communication we report the subsequent course of the three patients with osseous metastases described in the previous publication and present the results obtained in an additional group of eleven patients with osseous metastases from carcinoma of the breast.

A. S. (Case 2 in the preliminary report) developed metastatic disease of the lumbar spine and pelvis about ten years after a radical mastectomy. Testosterone therapy was instituted in April, 1945, and administered over a period of ten weeks for a total of 2,400 mg. After five weeks of therapy the patient became asymptomatic and maintained this status for five months. The osseous metastases became calcified.

Subsequent to the preliminary report she developed diplopia. Examination revealed a paralysis of the left upper eyelid and of the extraocular muscles supplied by the left third nerve. This was due to a central lesion, probably metastatic.

Testosterone therapy was reinstituted on Sept. 13, 1945. For a period of nine weeks 200 mg. of the androgen were administered twice a week for a total dose of 3,600 mg. The patient's general condition gradually deteriorated during this period. Roentgenographic studies of the lumbar spine and pelvis in November, 1945, revealed no significant changes upon comparison with previous views, that is the metastatic areas had remained calcified. Studies of the chest in December, 1945, revealed metastases in the lung parenchyma. About one month later the patient developed a metastatic nodule on the scalp. Her last visit to the clinic was in January, 1946. She was in the terminal stage of the disease.

S. K. (Case 3 of the original group) had a primary inoperable carcinoma of the breast with widespread metastasis to the cervical, dorsal, and lumbar spine, the pelvis, femora, ribs, and shoulder girdles. Testosterone therapy was instituted on March 10, 1945. Within two months there was a subsidence of the pain and a deposition of calcium in the lesions. The androgen was administered over a period of thirteen weeks for a total dosage of 4,100 mg.

Subsequent to the preliminary report the patient remained asymptomatic for approximately nine months. She then developed metastatic nodules in the skin of the neck and scalp. The postcervical lymph nodes became enlarged and hard. Roentgenograms made at this time revealed evidence of pulmonary metastasis and decalcification of the previously calcified osseous metastases.

Testosterone therapy was reinstituted and the patient received 25 mg. twice a week over a period of sixteen weeks. For the following four weeks she was given 200 mg. biweekly and 100 mg. twice a week for the subsequent fifteen weeks. The total dosage since reinstitution of the therapy was 5,250 mg. of the androgen.

The patient reported to the hospital for a period of thirteen months from the time the testosterone therapy was instituted. Roentgenograms at the end of this period disclosed

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the metastases to be predominantly osteolytic. The involvement was so extensive that little else but disease could be seen. She is now in the terminal stage of the disease.

The history of D. F. (Case 4 in the original group) will be recapitulated in greater detail because this patient's subsequent course presents some unusual features. A right radical mastectomy was performed in October, 1944, at the Memorial Hospital. The pathologic finding was a grade 3 infiltrating duct carcinoma with no node involvement. She received a cycle of postoperative roentgen therapy to the right axilla. Menstrual periods were regular. She was asymptomatic for five months following operation and no evidence of disease was found at periodic examinations.

In March, 1945, she experienced excruciating pain in the left hip radiating down the thigh. Roentgenographic investigation disclosed an area of destruction in the left ala of the sacrum. Testosterone therapy was instituted, 200 mg. being administered daily for one week and 25 mg. triweekly for the following ten weeks for a total of 2,150 mg. Subsequently, treatment was continued with 25 mg. twice a week for three months for a grand total of 2,750 mg.

The patient's pain diminished after two weeks of testosterone therapy. She was asymptomatic and had gained weight two months after the institution of the therapy. Roentgenograms in June and September, 1945, revealed progressive calcification in the metastatic area. She developed no other lesion. Amenorrhea had been present during this period. Therapy was discontinued in October, 1945. The patient had been asymptomatic for about six months and had continued to work during this interval.

One month after withdrawal of the testosterone the patient experienced an atypical menstrual period associated with discomfort in the left hip. A roentgenogram at this time revealed slight demineralization in the left wing of the sacrum. The pain in the left hip increased in intensity until at the end of a week it was excruciating. She could not eat, sleep, or walk. Her face was drawn and haggard. Large doses of codeine gave slight relief. The administration of 100 mg. of the androgen on Nov. 6, 1945, was followed by amelioration of pain within twenty-four hours. Another injection of 100 mg. two days later produced a further diminution of pain. For the ensuing week spotty vaginal bleeding occurred. The patient continued to receive 100 mg. triweekly for a total dose of 1,400 mg. since the reinstitution of the therapy. A roentgenogram taken at this time revealed evidence suggesting some bone regeneration in the area of destruction in the left ala of the sacrum. The patient again became asymptomatic and the therapy was discontinued.

Approximately five weeks later an irregular menstrual period, which consisted of spotting for two days, occurred. One week after the onset of the menses the patient again experienced pain in the left hip. Testosterone therapy was instituted this time without delay. Within twenty-four hours after an initial injection of 100 mg. there was considerable diminution of the pain. Two additional treatments of 100 mg. each were given on alternate days. At the end of one week she was asymptomatic. A roentgenogram made on Feb. 5, 1946, revealed further increase of calcification in the metastatic lesion of the sacrum.

After remaining asymptomatic for one month she experienced slight discomfort in the left hip. Menstruation began a few days later and the pain increased in intensity. The administration of 25 mg. of testosterone propionate on three alternate days produced no diminution of the pain. One hundred milligrams were then given on alternate days, and after the third injection the patient was asymptomatic.

Comment.—This patient is now in her second year of testosterone therapy, and has developed no further evidence of disease. She is asymptomatic as long as she is kept amenorrheic by the androgen. When testosterone proprionate is withdrawn there is a return of the menses accompanied by agonizing pain in the hip. The patient cannot sit, stand, or lie; sleep is impossible. These symptoms promptly disappear with the administration of 100 mg. on three alternate days. Twenty-five milligrams on three alternate days do not influence

the pain. The size of the individual dose is evidently an important factor. To date there have been five episodes successfully controlled by testosterone therapy.

The remainder of this communication reports a new series of eleven cases of advanced carcinoma of the female breast with osseous metastases treated with testosterone propionate.

CASE 1.—A. W. was a 60-year-old white woman. In August, 1945, a left radical mastectomy was performed at the Memorial Hospital. The pathologic diagnosis was infiltrating duct carcinoma, grade 3, metastatic to the axillary nodes at all levels. No postoperative roentgen therapy was administered. She was twelve years postmenopause.

The patient remained asymptomatic and apparently free of disease for about three months. She then returned to the clinic because of extreme pain in the right hip and thigh. Radiologic studies disclosed extensive metastasis to the pelvis and upper end of the shaft of the right femur (Fig. 1).

Fig. 1 (Case 1).—Numerous areas of metastasis are seen in the neck and shaft of the femur.

Therapy.—From Nov. 8, 1945, to Jan. 12, 1946, the patient received 200 mg. of testosterone propionate intramuscularly biweekly for a total dose of 3,600 mg. She received no other form of treatment.

Course.—At the end of two weeks of treatment the pain had decreased in intensity. At the end of the third week she no longer had sharp pain and could sleep at night without taking codeine. Some soreness and stiffness in the right thigh persisted. At the end of the fourth week the pain had entirely disappeared. Roentgenographic studies in February,

TABLE I. LABORATORY DATA, CASE 1

	11/1/45	12/4/45	1/3/46 (THERAPY DISCONTINUED)	2/21/46	3/12/46	4/4/46	5/20/46
Blood							
Hb.	80	84				82	89
R.B.C.	4.2	4.3				3.9	4.2
W.B.C.	6.0	8.1				7.3	4.1
Polys.	73	66				74	63
Monos.	2	4				2	3
Lymph	24	28				24	34
Alkaline phosphatase	3.7	5.3	7.6	8.0	8.0	5.0	7.0
Calcium	11.1	10.0	9.9	10.4	10.0	10.2	10.3
Chlorides	104	106	109	104	106	105	107
Phosphorus	3.84	3.16	2.90	3.96	2.82	3.26	3.86
Protein	6.6	6.5	6.6	7.0	7.7	6.9	6.9
Urine							
Sp. Gr.	1.014						1.020
Alb.	0						0
Sugar	0						0
Micr.	Occa. W.B.C.						0
Body weight (pounds)	158½	163¾	164	155		157½	157

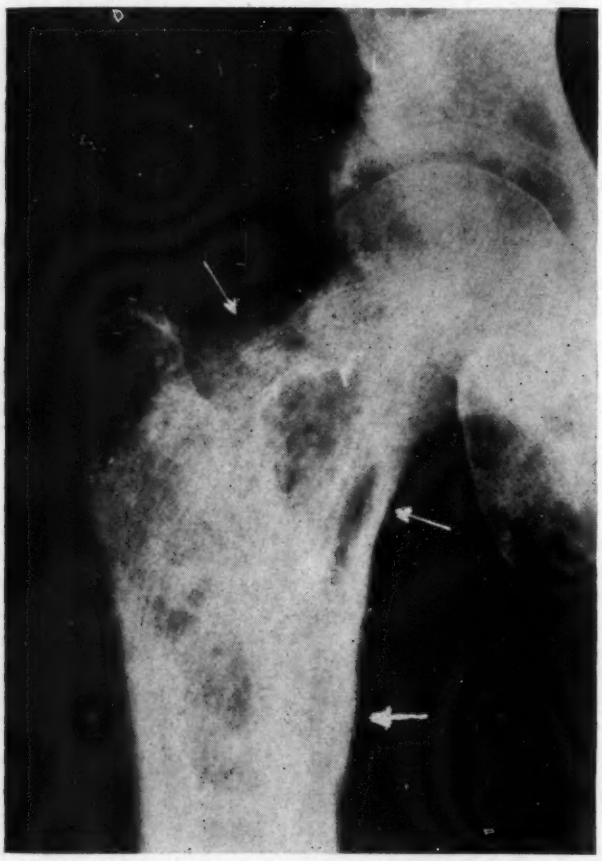

Fig. 2 (Case 1).—Roentgenogram made three months after the one shown in Fig. 1. During this period the patient received 3,500 mg. of testosterone propionate. The increased density produced by a deposition of calcium in the metastatic areas is well defined.

1946, revealed evidence of bone regeneration in the areas of destruction (Fig. 2). Roentgenograms taken in May, 1946, revealed no significant interval change. The patient has remained asymptomatic to date (July, 1946).

Comment.—The alkaline phosphatase exhibited a rise during the period that calcium deposition was demonstrated roentgenographically. Concomitant with the rise in phosphatase there was a drop in serum calcium. The elevation of the serum alkaline phosphatase continued after cessation of the androgen therapy. There was the customary increase in body weight which, however, was not retained after the therapy was discontinued. These changes are represented by the curves in Fig. 3.

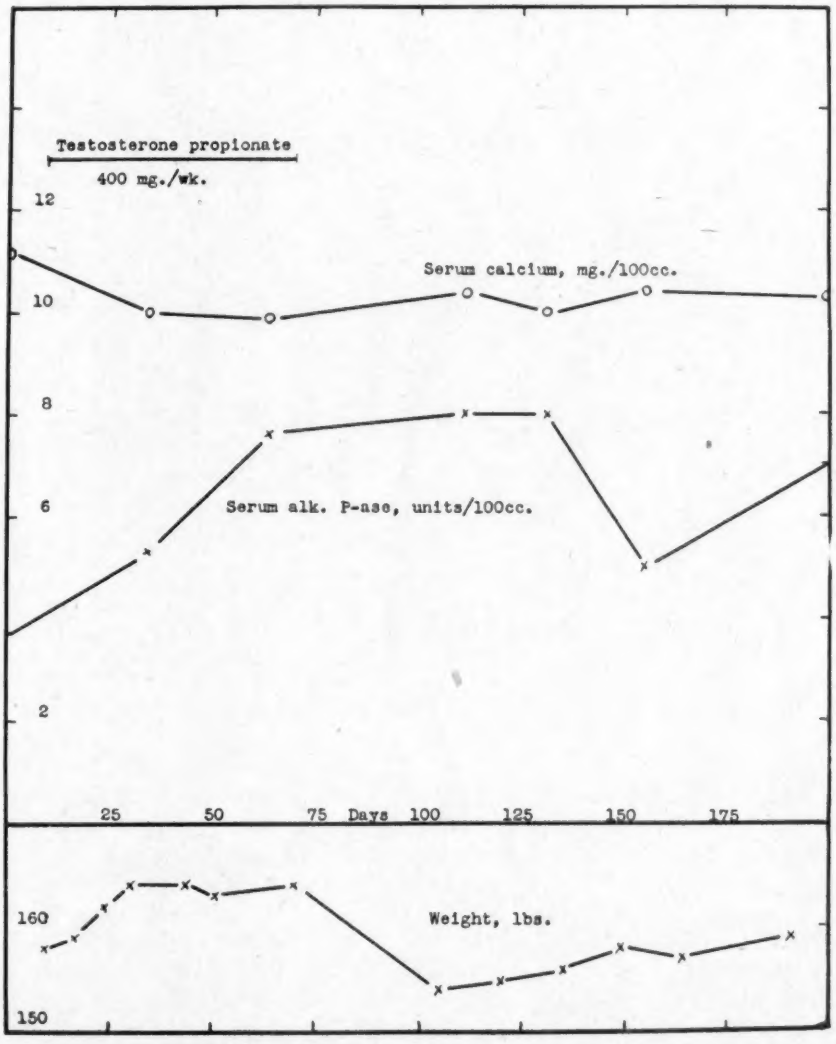

Fig. 3 (Case 1).—Graphic representation of the alterations in the serum calcium and alkaline phosphatase concomitant with the roentgenographic changes depicted in Fig. 2. There is a fall in the serum calcium and a rise in the alkaline phosphatase. The latter continues for a time after withdrawal of the testosterone. The initial body weight gain is lost after withdrawal of the androgen.

CASE 2.—V. P. was a 59-year-old white woman. She came to the Memorial Hospital in June, 1944, because of pain in the left arm. One year previously she had undergone a left radical mastectomy and postoperative roentgen therapy at another institution. Histologic study at the Memorial Hospital of a submitted slide of the tumor disclosed a comedo and infiltrating duct carcinoma, grade 2. Menses had ceased spontaneously when she was 52 years old.

Fig. 4 (Case 2).—Large areas of destruction are seen in the head, neck, and shaft of the humerus.

Roentgenographic investigation in July, 1944, revealed evidence of metastasis to the head and neck of the left humerus. The patient received 1,200 r. to the upper anterior and 800 r. to the upper posterior aspect of the left humerus from July, 1944, to August, 1944. The pain in the left shoulder subsided following irradiation but motion at the shoulder joint was markedly restricted. After remaining asymptomatic for about one year she returned in November, 1945, because of extreme pain in the left shoulder. There was associated muscle spasm. Radiologic examination Nov. 15, 1945, revealed evidence of metastasis in the shaft of the left humerus and of reactivation of the previously irradiated areas of metastases in the head and neck of this bone (Fig. 4).

Therapy.—From Nov. 24, 1945, to Jan. 12, 1946, the patient received 200 mg. of testosterone propionate biweekly for a total dose of 2,400 mg.

Course.—Three weeks from the time testosterone therapy was instituted the pain and the muscle spasm around the left shoulder had diminished markedly. The function of the left arm and shoulder continued to improve and the patient was able to perform household

duties and work her truck garden. She was asymptomatic after six weeks of treatment and has so remained until the present time, a period of six months.

A roentgenogram of the left humerus taken in March, 1946, six weeks after cessation of the testosterone therapy was reported as showing recalcification in the previously described metastatic areas (Fig. 5). There was no evidence that growth of the metastatic lesions had occurred since the previous roentgenogram was taken in November or that new areas of bone destruction had appeared.

Fig. 5 (Case 2).—Roentgenogram was made 3½ months after the one shown in Fig. 4. During this interval the patient received 2,400 mg. of testosterone propionate. Calcium has been deposited in all the metastatic areas. The cortex has regenerated in the head, neck, and involved portion of the shaft.

Comment.—This patient showed remarkable improvement. The body weight exhibited the usual rise during the androgen therapy and the drop when the treatment was withdrawn. There were no significant changes in the alkaline phosphatase such as were found in some of the other cases in the present series in which calcium deposition occurred. The testosterone therapy induced a deposition of calcium in a bone that had been previously irradiated. Although the amount of irradiation was small the results from the administration of the androgen would seem to indicate that previous irradiation of bone does not prevent it from recalcifying under the stimulus of the androgen.

TABLE II. LABORATORY DATA, CASE 2

	11/15/45	12/15/45	1/19/46 (THERAPY DISCONTINUED)	2/21/46	4/16/46
Blood					
Hb.	78	82	82		68
R.B.C.	3.9	3.8	3.9		3.3
W.B.C.	6.1	5.6	9.8		6.0
Polys.	51	73	80		61
Monos.	2	2			4
Lymph	46	25	20		33
Calcium	11.2	10.8	10.9	11.1	10.2
Chlorides	95	101	101	103	105
Alkaline phosphatase	3.0	2.5	3.1	4.2	3.4
Phosphorus	2.94	2.44	2.46	2.86	3.10
Protein	7.2	7.3	7.3	7.5	6.9
Urine					
Sp. Gr.	1006	1021			1020
Alb.	0	1+			0
Sugar	0	0			0
Micr.	Occa. R.B.C.	Occa. R.B.C.			Occa. W.B.C.
Body weight (pounds)	163	169½	171	162½	161

CASE 3.—M. K. was a 59-year-old white woman. In 1932 a left radical mastectomy was performed at another institution. The pathologic diagnosis at the Memorial Hospital of a submitted slide was infiltrating carcinoma simplex. The patient received a cycle of postoperative roentgen therapy at the Memorial Hospital. After remaining free of disease for five years (1937) she developed a metastatic nodule in the mastectomy scar. The nodule was excised at this institution. Histopathologic examination revealed it to be recurrent mammary carcinoma.

The patient remained free of disease for another period of six years (1943). At this time another nodule appeared in the mastectomy scar which regressed with radiation therapy administered at the Memorial Hospital.

In July, 1945, thirteen years after mastectomy the patient developed pain in the right shoulder. A roentgenogram made at the Memorial Hospital in October, 1945, disclosed areas

TABLE III. LABORATORY DATA, CASE 3

	10/6/45	11/20/45	12/11/45	1/10/46	1/19/46	2/25/46	4/9/46
Blood							
Hb.	76		93				62
R.B.C.	3.5		4.5				3.1
W.B.C.	4.5		6.0				6.6
Polys.	64		59				80
Monos.			2				1
Lymph	36		39				19
Alkaline phosphatase	3.8	6.2	3.8	4.2	3.7	3.6	4.2
Calcium		10.8	11.6		10.0	10.0	10.1
Chlorides		105	103			104	104
Phosphorus	3.44	2.02	3.16	2.98	2.48	3.09	3.32
Protein		7.1	7.3	8.1	7.6	7.5	7.7
Urine							
Sp. Gr.	1.015		1.016				1.016
Alb.	0		Trace				0
Sugar	0		0				0
Micr.	Epith.		Occa. pus clump				0
Body weight (pounds)	189	196½	195½	190½	192	188	192½

of destruction in the head of the right scapula and in the right seventh rib (Fig. 6). The lumbar spine and pelvis were negative for evidence of metastasis.

Therapy.—The patient received 100 mg. of testosterone propionate triweekly from Oct. 9 to Nov. 17, 1945, for a total dose of 1,300 mg. Treatment was continued with 25 mg. administered triweekly from Nov. 24, 1945, to Jan. 15, 1946. From April 6, 1946, to June 8, 1946, an additional 600 mg. were administered. The all-inclusive dose was 2,475 mg. No other form of therapy was employed.

Course.—After the first two weeks of treatment there was some diminution in the pain. At the end of the third week the pain had completely disappeared and she could move her arm freely. When the total dose had reached 1,300 mg. the patient complained of dizziness. Examination revealed some puffiness about the eyes and moderate pretibial edema. Because of this reaction the dose was reduced to 25 mg. triweekly. The dizziness and edema promptly subsided. There was at no time any return of the pain.

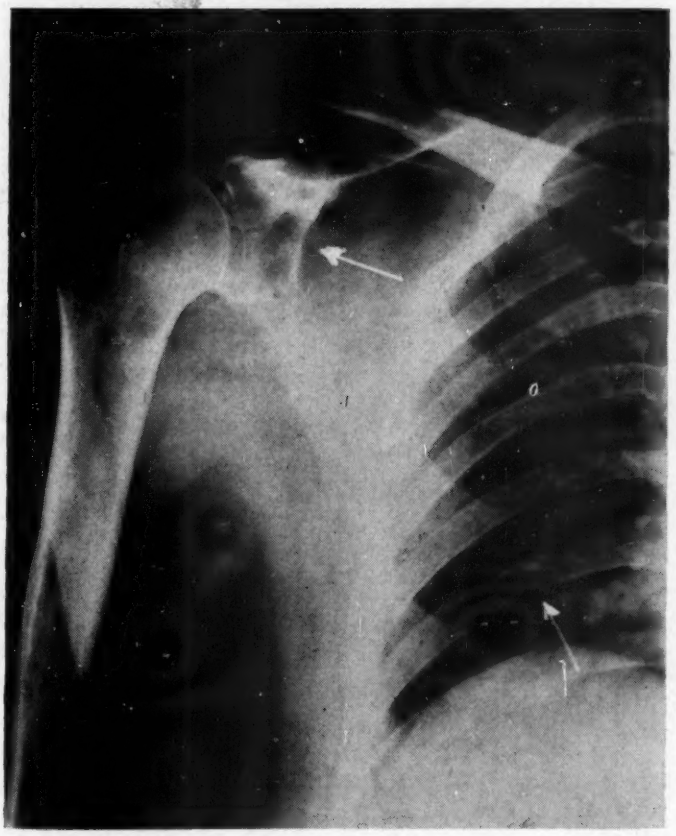

Fig. 6 (Case 3).—The head of the scapula is almost completely involved by the metastatic process. There is a small area of destruction in the seventh rib.

Radiographic studies made in January, 1946, three months after the institution of the androgen therapy revealed pronounced recalcification of the metastatic areas in the right scapula and right seventh rib (Fig. 7). Testosterone therapy was withdrawn and the patient remained asymptomatic for the following three months. Then the pain in the right shoulder recurred. A roentgenogram taken April 9, 1946, revealed that the calcified area of metastasis in the head of the scapula had become a little more osteolytic. Studies of the lumbar spine and pelvis revealed evidence of metastasis. There were, however, no symptoms referable to these regions. Testosterone therapy was again instituted and the patient became asymptomatic within three weeks.

Comment.—Metastasis which developed in the scapula thirteen years after mastectomy yielded satisfactorily to testosterone therapy. The lesion became reactivated and pain recurred when the androgen was withdrawn. Reinstitution of the therapy caused a disappearance of the pain.

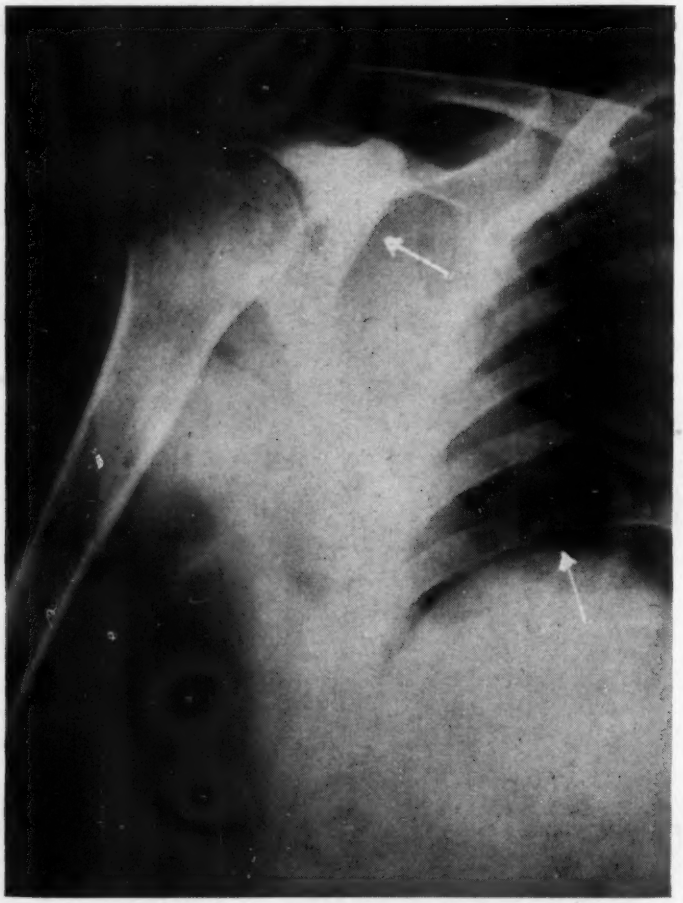

Fig. 7 (Case 3).—Roentgenogram taken three months after that shown in the previous figure reveals the pronounced calcification that has taken place in the metastatic lesions. The patient had received 1,785 mg. of testosterone propionate during this period.

CASE 4.—M. W. was a 43-year-old colored woman. In March, 1945, a right radical mastectomy was performed at the Memorial Hospital. The pathologic report was infiltrating duct carcinoma, grade 4, metastatic to all levels. She received a cycle of postoperative roentgen therapy to the right axilla through three ports. The menses at that time were regular.

One month after operation the patient experienced pain in the right hip. Roentgenographic studies of the lumbar spine and pelvis failed to reveal evidence of metastasis. Nevertheless, roentgen castration was induced because the high grade of malignancy of the neoplasm, the extent of the node involvement, and the suggestive pain in the hip made this procedure seem advisable.

The pain in the hip subsided following castration and the patient remained asymptomatic and apparently free of disease for approximately six months. She returned to the clinic in January, 1946, complaining of pain in the left side of the head and ribs, and of inability to flex the back because of pain in the lumbar region. There was pronounced left exophthalmos.

Roentgenographic investigation revealed irregular areas of bone destruction in the skull suggestive of carcinoma metastasis and evidence of metastasis to the twelfth dorsal and lumbar vertebrae.

Therapy.—Testosterone therapy was instituted on Jan. 24, 1946. The patient received 100 mg. of the androgen bi-weekly for a total dose of 1,000 mg. No other type of therapy was employed.

Course.—At the end of the third week of treatment the patient's back pain had regressed markedly. She was able to walk and to flex the spine with very little discomfort. There was continued symptomatic improvement during the five-week period that the patient attended the clinic. She then failed to return for one month. Examination at the end of this interval revealed the exophthalmos to be present but the patient was asymptomatic.

Roentgenograms made in April, 1946, revealed the metastases in the lumbar and dorsal vertebrae to be predominantly osteoblastic with several dense structureless areas of bone present in the second and sixth lumbar vertebrae. Chemical studies revealed a rise in the alkaline phosphatase.

Comment.—Despite radiologic castration this patient developed osseous metastases. There was a prompt response to testosterone therapy. Although the androgen was withdrawn after five weeks the serum alkaline phosphatase continued to rise. It would appear that the stimulus initiated by the androgen continues after its withdrawal.

TABLE IV. LABORATORY DATA, CASE 4

	1/26/46	2/26/46 (THERAPY DISCONTINUED)	4/16/46
Blood			
Hb.	62		
R.B.C.	3.2		
W.B.C.	5.0		
Polys.	67		
Monos.	5		
Lymph	28		
Alkaline phosphatase	5.1	7.0	8.5
Calcium	10.2	11.1	11.0
Chlorides	103	104	106
Phosphorus	3.48	2.55	3.84
Protein	8.6	7.9	8.1
Urine			
Sp. Gr.			1.012
Alb.			0
Sugar			0
Micr.			Occa. W.B.C.
Body weight (pounds)		152	142

CASE 5.—M. B. was a 58-year-old white woman. In 1944, a right radical mastectomy was performed at another institution. The pathologic finding was an infiltrating duct carcinoma, grade 3. Three years after the operation the patient developed pain in the lower back and hips. Roentgenograms taken at this time disclosed metastatic disease in the lumbar spine, pelvis, and upper femora.

In June, 1945, at another institution, the patient received 1,255 r. to the posterior pelvis and 418 r. to the lumbar spine with amelioration of the pain. The voltage employed was 400 kv. The pain recurred in October, 1945, and, at the same institution, the patient received 1,250 r. to the left hip and thigh anteriorly and 210 r. to the right hip posteriorly. The pain persisted, therefore an additional 840 r. were administered to both femora in November, 1945. The patient obtained no relief.

Therapy and Course.—Beginning Dec. 1, 1945, at the Memorial Hospital the patient received 100 mg. of testosterone propionate daily for a total dose of 1,300 mg. She was then able to walk up and down stairs unaided whereas two weeks previously she had entered the hospital in a wheel chair.

She returned to her home in a distant city where she continued to receive 100 mg. of the androgen six days a week for three weeks. Treatment was then continued with 25 mg. triweekly until May 7, 1946, for a grand total of 4,150 mg. since the institution of the androgen therapy in December.

Roentgenographic studies at the Memorial Hospital in June, 1946, revealed a slight increase in the extent of the metastases observed in previous roentgenograms. They were, however, slightly more osteoblastic in character. Some stiffness persisted in the hips but there was no pain.

Comment.—Testosterone produced striking relief of pain after irradiation was no longer effective. Repeated blood chemical studies revealed a progressive elevation of the serum alkaline phosphatase. The patient developed a progressively severe anemia which was probably due to the suppression of hematopoiesis by metastases in the long bones.

TABLE V. LABORATORY DATA, CASE 5

	11/28/45	12/13/45	2/19/46	5/22/46
Blood				
Hb.	69	75		58
R.B.C.	3.5	3.7		3
W.B.C.	6.8	5.2		6.7
Polys.	78	76		62
Eosin.		2		
Monos.	4	10		8
Lymph	18	12		23
Immature forms				7
Alkaline phosphatase	3.8	5.2	6.4	9.4
Calcium	10.4	10.2	10.8	12.1
Chlorides	97	103	101	101
Phosphorus	4.30	3.30	4.22	4.70
Protein	6.3	6.3	7.0	7.2
Urine				
Sp. Gr.	1.020	1.010		
Alb.	0	0		
Sugar	0	0		
Micr.	Occa. R.B.C.	Neg.		

CASE 6.—H. K. was a 40-year-old white woman. In December, 1943, a radical mastectomy for infiltrating duct carcinoma, grade 3, was performed at the Memorial Hospital. She received a cycle of postoperative irradiation because the axillary lymph nodes were involved. Menstrual periods were irregular at the time of operation and shortly thereafter she underwent a spontaneous menopause.

The patient began to experience pain in the lumbar region radiating down the thighs in March, 1945, more than one year following operation. Roentgenograms revealed evidence of metastasis to the lumbar spine and pelvis. In April, 1945, the right side of the pelvis received 800 r. to each of three ports, an anterior, a posterior, and a lateral. In June, 1945, 1,200 r. were administered to the lumbar spine and sacrum and in July, 1945, 400 r. to each of two anterior and 800 r. to each of two posterior pelvic ports. The voltage employed was 250 kv. There was some diminution of the pain following roentgen therapy. It soon became severe again. Later she developed pain in the ribs and right shoulder. Roentgenograms taken October, 1945, of the right shoulder and the chest revealed widespread metastasis to practically all of the ribs, the vertebrae, and the right humerus and glenoid fossa.

TABLE VI. LABORATORY DATA, CASE 6

	10/15/45	12/20/45	1/17/46	2/17/46	3/28/46	4/25/46
Blood						
Hb.	56	60	58		65	
R.B.C.	2.9	2.8	3.2		3.0	
W.B.C.	5.3	5.6	5.4		4.0	
Polys.	71	68	56		67	
Monos.	2	1	2		1	
Lymph	23	31	40		31	
Alkaline phosphatase	8.4	14.7	12.7	10.1	10.8	4.4
Calcium	11.0	10.7	9.9	10.1	10.4	11.1
Chlorides		104		105	106	102
Phosphorus	3.98	3.00	3.24	3.64	3.76	3.84
Protein		6.2	6.4	6.2	6.9	6.8
Urine						
Sp. Gr.	1.012				1.022	
Alb.	Trace				Trace	
Sugar	0				0	
Micr.	Occa. W.B.C.				Occa. R.B.C.	
Body weight (pounds)	128	133	135	137½	131½	

Therapy.—Testosterone therapy was instituted on Nov. 6, 1945. The patient received 200 mg. of the androgen twice a week over approximately twelve weeks for a total dose of 3,200 mg. There were two absences of about two weeks each from the clinic during this period. Following this she received 25 mg. twice a week for seven weeks for an additional dose of 375 mg. The dosage was then increased to 200 mg. twice a week for a period of six weeks for a grand total of 6,175 mg.

Course.—The patient was asymptomatic at the end of one month of therapy and maintained this status for four months. She then developed a sensation of numbness over the left side of the mandible. Roentgenograms of the mandible and skull at this time revealed metastases, predominantly osteoblastic, to the vault of the skull. At this time the dose was increased from 25 to 200 mg. biweekly. Roentgenograms of the chest, lumbar spine, pelvis, and right shoulder girdle were taken at monthly intervals from October, 1945, to June, 1946. A slight increase in the number and extent of the osseous metastases which became more osteoblastic in character was noted. Aside from a sensation of numbness in the region of the chin the patient has been asymptomatic for seven months.

Comment.—Irradiation did not appreciably influence the pain. The administration of testosterone was followed by a rise in the serum alkaline phosphatase and a disappearance of the pain. The metastases became more osteoblastic in character, which may account for the subsidence of the pain.

TABLE VII. LABORATORY DATA, CASE 7

	7/31/45	9/27/45	10/15/45	11/15/45	12/11/45
Blood					
Hb.	75	69	65	76	
R.B.C.	3.5	3.4	3.2	3.4	
W.B.C.	4.3	6.5	7.6	6.5	
Polys.	46	33	58	41	
Monos.	1	3	6	2	
Lymph	53	64	36	57	
Alkaline phosphatase	4.7	9.8	13.1	8.9	5.2
Calcium	11.1	11.1	9.9	9.8	10.1
Chlorides				103	99
Phosphorus	3.84	2.20	2.26	2.34	2.86
Protein				6.8	7.1
Urine					
Sp. Gr.		1.018			
Alb.		Trace			
Sugar		Trace			
Micr.		Many R.B.C.			
Body weight (pounds)	125	130½	132¼	130¾	124

CASE 7.—D. M. was a 45-year-old white woman. In January, 1940, a right radical mastectomy for a grade 2 infiltrating duct carcinoma was performed at the Memorial Hospital. There was no axillary lymph node involvement. For over five years she was asymptomatic and apparently free of disease. She then developed pain in the lumbar spine. Roentgenograms taken July, 1945, revealed evidence of extensive metastasis to the lumbar spine and pelvis. Menstrual periods were regular.

Therapy.—Testosterone therapy was instituted on Aug. 7, 1945. For a period of two months 200 mg. of the androgen were administered biweekly for a total dose of 3,200 mg. Treatment was then continued with 25 mg. triweekly for an additional six weeks until a grand total of 3,650 mg. had been administered.

Course.—At the end of the first month of treatment the patient was asymptomatic aside from occasional discomfort and stiffness in the left hip when climbing stairs. A

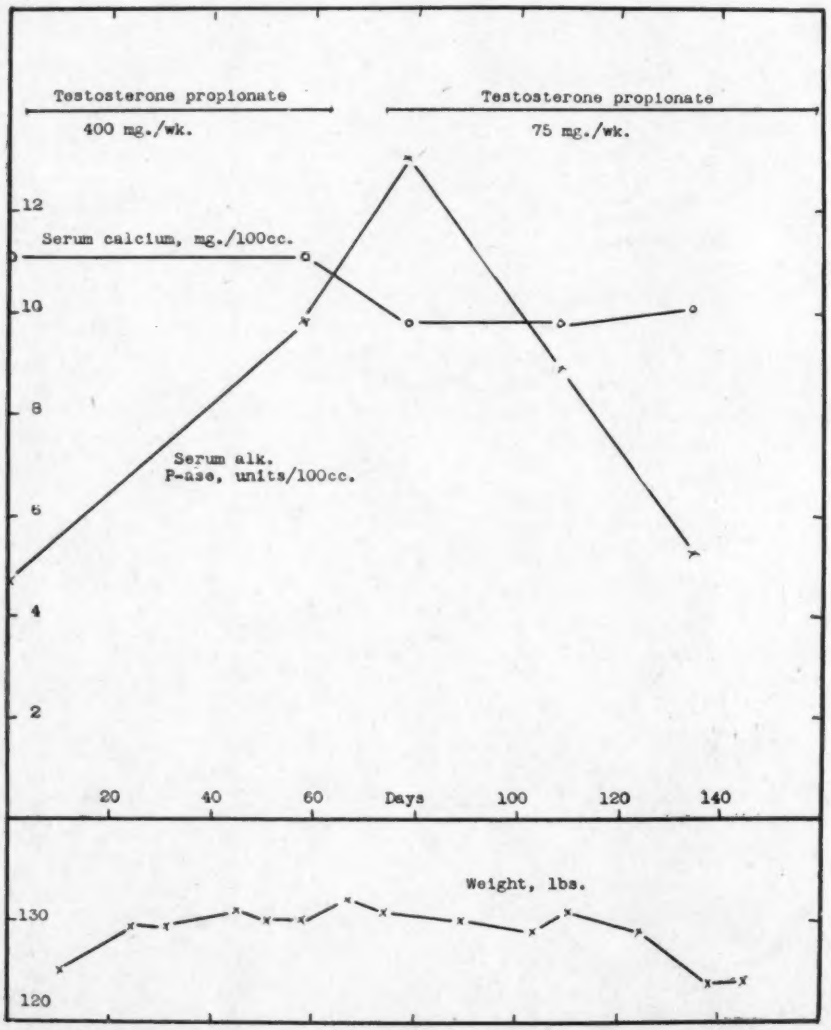

Fig. 8 (Case 7).—Graphic representation of the changes in the serum calcium, alkaline phosphatase, and body weight produced by the administration of testosterone propionate. Although there were no significant roentgenologic alterations concomitant with the chemical changes, the patient's pain disappeared. At the end of four months of therapy she developed evidence of pulmonary metastasis. About this time the weight gain induced by the androgen was lost.

roentgenogram made Nov. 24, 1945 disclosed no significant change upon comparison with that taken in July, 1945.

In December, 1945, four months after the institution of the testosterone therapy numerous skin nodules were observed throughout the scalp. An excisional biopsy of one of the nodules was reported as metastatic mammary carcinoma. A roentgenogram of the lumbar spine and pelvis taken at this time revealed the degree of involvement to be somewhat more extensive and the lesions somewhat more osteolytic in character than at the examination in November, 1945. The patient failed to return to the clinic and upon investigation it was found that she had developed pulmonary metastases.

Comment.—Although there was a striking rise in the serum alkaline phosphatase (Fig. 8) there was no roentgenologic evidence of calcification in the osseous metastases. Subsequently, there was a slight increase in the osteolytic character of the lesions. The patient's condition deteriorated rapidly after the appearance of pulmonary metastases.

CASE 8.—G. W. was a 55-year-old white woman. In July, 1946, a right radical mastectomy was performed at another institution. She came to the Memorial Hospital six months later because she noticed some "lumps" in the right axilla. Menopause had occurred ten years previous to the mastectomy.

Examination in January, 1946, revealed several subcutaneous nodules in the right axilla. An excisional biopsy of one of these nodules was reported as metastatic mammary carcinoma. Roentgenograms disclosed numerous areas of metastasis in the lumbar vertebrae, the pelvis, and the upper end of the left femur. There was no evidence of metastasis to the lungs. The patient was asymptomatic.

Therapy.—Testosterone therapy was instituted on Feb. 2, 1946. Relatively small doses of the androgen, 50 mg. biweekly, were employed because the osseous lesions were causing no symptoms. In addition 5 Gm. of calcium gluconate and 20 drops of vitamin D were taken daily by the patient during the period of therapy. The androgen was administered over a period of thirteen weeks, with occasional lapses, for a total of 1,150 mg.

Course.—The patient developed severe pain in the left hip two weeks after the androgen therapy was instituted. Despite considerable pain she returned for treatment after one week's absence. Roentgenographic studies at this time revealed an increase in the size and extent of the metastatic lesions. After three weeks of additional testosterone therapy the

TABLE VIII. LABORATORY DATA, CASE 8

	1/31/46	3/5/46	4/2/46	4/30/46
Blood				
Hb.	79	74		72
R.B.C.	4.0	3.6		4.1
W.B.C.	7.7	6.2		12.6
Polys.	47	63		58
Eosin.	1	3		
Monos.	2	2		6
Lymph	50	32		36
Alkaline phosphatase	4.5	5.5	6.2	10.1
Calcium	11.7	12.2	10.7	11.4
Chlorides	105	107	106	102
Phosphorus	3.62	3.64	3.06	3.54
Protein	6.8	6.9	6.7	7.2
Urine				
Sp. Gr.	1.004			1.000
Alb.	0			1+
Sugar	0			0
Micr.	0			Occa. casts
Body weight (pounds)	137	140	143	139

pain disappeared and she remained asympomatic for one month. She then developed a cough. A roentgenogram revealed a large amount of fluid in the left side of the chest and metastatic lesions in two ribs. The lesions in the pelvis were essentially unchanged. Shortly after, she failed to return to the clinic.

Comment.—This case is unusual in that the androgen at first appeared to activate the lesions and later to inactivate them. The activation by the androgen is apparently similar to the phenomenon described by Farrow and Woodard.[2]

CASE 9.—J. L. was a 39-year-old white woman. In June, 1944, a right radical mastectomy was performed at the Memorial Hospital. The pathologic diagnosis was comedo and infiltrating duct carcinoma, grade 3. She received a postoperative cycle of roentgenotherapy to the right axilla. Menstrual periods were regular.

There was no evidence of recurrent disease for almost two years. The patient then began to experience pain in the left shoulder and lower back and was unable to flex the lumbar spine. Roentgenograms taken in March, 1946, revealed evidence of metastasis to the twelfth dorsal and fifth lumbar vertebrae, to the shafts of both femora, and to the glenoid fossa of the left scapula.

Therapy.—From March 30, 1946, to May 18, 1946, she received 50 mg. of testosterone proprionate biweekly for a total of 800 mg. From June 11, 1946, to June 18, 1946, she received three injections of 100 mg. each for a grand total of 1,100 mg. No other type of therapy was employed.

Course.—Within one month from the time androgen therapy was instituted she was asymptomatic, able to flex the lumbar spine without discomfort, and wished to return to work. Roentgenograms at this time, April 30, 1946, revealed increased density in the previously described areas of destruction in the right upper femur and in the left scapula.

The patient remained asymptomatic for one month during which no therapy was administered. Then the pain in the lower back recurred, associated with nausea and vomiting. Abdominal examination failed to reveal any palpable viscera or masses. Roentgenologic studies made June 8, 1946, revealed an increase in the size and extent of the osseous metastases. Blood chemical studies disclosed a suggestive elevation of the serum calcium.

Shortly thereafter the patient reported bloody vaginal spotting. This was the first menstrual period since the institution of androgen therapy ten weeks previously. The vomiting continued and the back pain became progressively worse. Therefore, 100 mg. of testosterone propionate were administered on alternate days for three doses. The vaginal bleeding ceased but the pain, nausea, and vomiting became accentuated. Blood chemical studies at

TABLE IX. LABORATORY DATA, CASE 9

	3/18/46	4/23/46	5/22/46	6/11/46	6/18/46	6/22/46
Blood						
Hb.	80		73			
R.B.C.	3.8		3.6			
W.B.C.	3.4		4.4			
Polys.	63		57			
Monos.	1		3			
Lymph	36		40			
Alkaline phosphatase	6.8	5.4	5.9	5.8	4.6	6.3
Calcium	11.0	10.4	10.5	12.4	13.4	15.0
Chlorides	105	111	111	100	100	
Phosphorus	3.50	2.64	3.62	3.56	4.46	4.66
Protein	7.1	6.9	7.0	7.3	7.1	7.7
Urine						
Sp. Gr.	1.016					
Alb.	0					
Sugar	0					
Micr.	Neg.					
Body weight (pounds)	115	115¼	115¼		105½	

this time revealed a hypercalcemia therefore the androgen therapy was terminated. One week later a further elevation of the serum calcium was found. The nausea and vomiting were uncontrollable. The patient's condition was so poor that she was institutionalized.

Comment.—This case differs from the previous one in that the reactivation of the lesions occurred after the androgen had been withdrawn. The serum calcium continued to rise despite cessation of testosterone therapy which is contrary to our previously reported findings[1] and to those of Farrow and Woodard.[2]

CASE 10.—A. K. was a 62-year-old white woman. In 1942, a right radical mastectomy was performed at the Memorial Hospital. The pathologic diagnosis was a gelatinous adenocarcinoma, grade 2, nodes clear. The patient was apparently free of disease for about three years. She then developed pain in the cervical region and the right hand. Roentgenograms taken in May, 1945, revealed metastasis to the cervical vertebrae but no evidence of involvement of the bones of the hand. She was given 1,200 r. high voltage x-irradiation to the cervical region with some diminution of the pain. The pain and the swelling in the right hand increased. Roentgenograms taken in July, 1945, revealed evidence of destruction of the right fourth metacarpal consistent with metastasis.

Therapy.—Testosterone therapy was instituted Aug. 2, 1945. The patient received 200 mg. biweekly for seven weeks for a total dose of 2,800 mg.

Course.—The swelling and pain in the right hand grew progressively worse. She developed a lesion on the scalp which was presumably metastatic mammary carcinoma. The patient died of the disease one week after the termination of the androgen therapy.

CASE 11.—A. R. was a 53-year-old white woman. In 1941, a left radical mastestomy was performed at the Memorial Hospital. The pathologic examination revealed infiltrating duct carcinoma, grade 2, no lymph node involvement. Roentgenographic studies of the chest, lumbar spine, and pelvis were negative for evidence of metastasis.

Following the operation the patient remained apparently in good health for about four years. In May, 1945, during the course of a routine checkup at the Memorial Hospital, left supraclavicular nodes were palpated. An aspiration biopsy was reported as carcinoma. The palpable nodes disappeared completely with roentgen therapy. The patient remained asymptomatic for approximately five months. She then developed pain in the right side of the chest. Roentgenograms taken in October, 1945, revealed areas of metastasis in the dorsal spine and ribs.

Therapy.—From Nov. 1, 1945, to Jan. 31, 1946, the patient received 100 mg. of testosterone propionate biweekly for a total dose of 2,400 mg. Following that she received 25 mg. biweekly until March 7, 1946, for a grand total of 2,650 mg. No other form of therapy was administered.

Course.—Two weeks after the institution of testosterone therapy the patient was asymptomatic and returned to work. She had occasional discomfort in the left hip. Roentgenograms taken Jan. 15, 1946, revealed the metastases to be a little more extensive but more osteoblastic in character. Five months after the androgen therapy was instituted she

TABLE X. LABORATORY DATA, CASE 11

	10/25/45	11/27/45	1/10/46	2/19/46
Calcium	11.3	10.6	10.9	11.0
Chloride		101		100
Alkaline Phosphatase	5.0	5.2	8.5	9.7
Phosphorus	3.96	2.68	2.98	3.22
Protein		6.6	7.2	7.4
Body weight (pounds)		163	165	162½

began to have abdominal pain. Upon examination an enlargement of the liver, evidently due to metastasis, was found.

Comment.—There was an elevation of serum alkaline phosphatase concomitant with osteoblastic changes in the metastases. The change in the character of the metastases may be the factor that caused a diminution in the pain. The general condition of the patient deteriorated rapidly after the onset of the liver enlargement.

SUMMARY AND CONCLUSIONS

Since the preliminary report on the use of testosterone propionate in advanced carcinoma of the female breast, eleven additional patients with osseous metastases have been treated with the androgen. These patients ranged in age from 39 to 62 years. With three exceptions they were treated exclusively with testosterone propionate administered intramuscularly. The exceptions were patients in whom previous irradiation of osseous metastases had failed to control the pain. In so far as these patients improved with subsequent androgen therapy it would seem that repeated irradiation of bones does not destroy their power to react to the androgen.

Symptomatic improvement, evident within two weeks after the institution of the therapy, was manifested by eight patients. Six patients revealed roentgenologic evidence of calcification in the metastatic areas. In some patients these changes were discernible four to six weeks after institution of the therapy. In some instances as bone density increased there was a drop in the serum calcium indicating either a deposition of this element in the metastatic areas or a decrease in osteolysis. There was a rise in the serum alkaline phosphatase in eight patients. In the absence of liver disease an elevation in serum alkaline phosphatase indicates bone growth or an attempt at bone regeneration. It appears likely that, during the period of imbalance following the institution of endocrine therapy, some mechanism, perhaps involving the pituitary or the suprarenal, stimulates osteoblastic activity and alkaline phosphatase production.

The bone lesions appeared to remain quiescent for a variable length of time after the androgen therapy was terminated. If pain recurred it could be controlled by additional androgen therapy. It would appear that in many instances a favorable status may be maintained until pulmonary or liver metastasis appears. When this occurs the patient rapidly retrogresses and dies within a relatively short time despite the continued administration of the androgen.

The favorable results in the present series have been obtained with smaller amounts of testosterone propionate than were used in patients previously reported.[1] The dosages employed successfully in the present investigation were 100 and 200 mg. biweekly and 100 mg. triweekly. It is suggestive that the least satisfactory results were obtained when biweekly doses of 50 mg. were employed. The treatment was usually continued until the patient became asymptomatic. It is probable that therapy can be terminated before this point is reached and yet have the symptomatic improvement and the rise in the alkaline phosphatase continue.

The androgen induced amenorrhea but the menses returned after this therapy was withdrawn. One patient who was asymptomatic as long as she was kept amenorrheic by testosterone propionate developed pain in the metastatic area when the androgen was withdrawn and the menses returned. In some patients acne appeared on the neck, shoulders, and chest. The other undesirable sequelae were facial hirsutism and deepening of the voice. In one patient there was transient edema of the face and legs. An increase in libido was noted in many patients.

All of the patients exhibited a gain in body weight during the initial period of androgen medication. When the therapy was terminated much of this weight was lost. The gain in weight was probably due to protein nitrogen retention by the tissues rather than to fluid retention.[3] In the majority of cases there was no significant alteration in the blood, serum protein, chlorides, or urine to judge by routine examinations.

From the results obtained in the present investigation it would appear that testosterone propionate is of value in the treatment of osseous metastases secondary to carcinoma of the female breast.

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ALKAPTONURIC ARTHRITIS

Cause for Free Intra-articular Bodies

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AN UNUSUAL cause for the formation of free bodies in a joint cavity is a disturbance in the catabolism of the proteins tyrosine and phenylalanine. In patients with this disorder, these proteins which are present in food and tissues are not completely metabolized and form an intermediate product known as homogentisic acid—an alkapton body. This abnormality in metabolism known as alkaptonuria may be due to an inborn error of catabolism of proteins or to prolonged use of phenol dressings for ulcers or wounds. The homogentisic acid which is deposited in tissues and excreted in the urine causes the color of the urine to change to brown or black on exposure to air. Associated with the formation of this acid, there is a tendency either for conversion of these alkapton bodies into pigment in situ or for a deposition of ocher pigmented granules into either relatively avascular tissues or into those with poor metabolism.[1] Thus, the articular cartilage, tendons, ligaments, intervertebral discs, fibrocartilage, sclerae, atherosclerotic plaques, etc., may become pigmented, resulting in a condition known as ochronosis. Such depositions have also been known to occur in epithelial cells and in smooth, striated, and cardiac muscle. For some unknown reason when musculoskeletal tissues are the seats of such pigment deposition, calcification or ossification may also occur at these sites. The articular cartilages, intervertebral discs, and other cartilaginous or ligamentous tissues may become calcified or ossified or may undergo prematurely, occasionally as early as childhood, degenerative changes commonly seen in ordinary osteoarthritis.[2] When the arthritic process affects the knee or any other large joint, there may be an associated formation of free bodies in the articular cavity.[3]

This paper is presented in order to record the case of a patient who had free bodies in one of the knees as a result of this error in metabolism.

CASE REPORT

A 42-year-old soldier was admitted to this hospital because of a pain in the left knee for thirty days. One month prior to this visit to the institution, the patient slipped on the ice and twisted the left leg. The left knee became very painful and enlarged, to a degree which interfered with locomotion. For this reason, he was admitted to the hospital for treatment. On further questioning the patient stated that he had had pain in the lower back for the past five years. During this period of time he could not fully bend the trunk or lift heavy objects without experiencing local pain. He occasionally suffered from sprains in the ankles, but had never had any severe pains or swellings of any of the joints of the upper or lower extremities. After the completion of the physical examination, the patient was questioned about the color of the urine. He stated that for the past five years the urine had turned brownish-black when it was exposed to the air. He denied the use of carbolic acid dressings or ointments. As for family history, he did not know whether his

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father or mother had any difficulty with the back or whether they had noted the presence of brownish or blackish coloration of the urine. There were no other living members of the family.

On physical examination it was noted that this soldier walked with a definite limp. The trunk was stooped slightly forward and this resulted in an obliteration of the lumbar lordosis. A diffuse ruddiness of the face and a slate-colored pigmentation of the auricles were observed. No gross discoloration of the cornea or sclera was present. The orthopedic examination revealed that the range of flexion of the trunk was possible to an angle of 120 degrees. Extension of the trunk was restricted to the neutral or vertical plane. Tenderness was experienced on pressure over the lumbosacral area. A 15 degree restriction was encountered to straight leg raising on the right as well as on the left lower extremities. There was also a 10 degree restriction to complete flexion of the right thigh. Internal rotation of either thigh was possible only to the neutral plane. Combined or total abduction of the thighs was not impaired.

Examination of the knees revealed the absence of any effusion. Crepitation was felt and heard in both knees but to a greater extent on the left side. Direct pressure made over the left patella caused discomfort and tenderness. The left leg could be actively extended to an angle of 180 degrees and flexed to an angle of 50 degrees. These movements caused pain in the left knee joint. The right knee presented a normal range of motion.

Examination of the ankles revealed a thickening of the left tendo achillis at a level of about one inch proximal to its attachment to the os calcis. The range of motion at the ankles was within normal limits. As far as the upper extremities were concerned, 15 degrees restriction in motion was noted to complete abduction of the arms in the coronal plane. Otherwise, the other joints of the upper extremity revealed nothing unusual.

The pulsations of the radial, dorsalis pedis, and posterior tibial arteries were palpable. There was no evidence by palpation of any calcification of these blood vessels. Ophthalmoscopic examination revealed that the optic disc and retina were normal in appearance. Slit lamp examination demonstrated the presence of brownish-black small accumulations of pigment in the stroma of the bulbar conjunctiva of the left eye at the region of nine o'clock. The pigment was deposited in two rows about 3 to 4 mm. from the limbus. A few of the deposits were of macroscopic size. A single deposit was found in the conjunctiva of the right eye at the region of nine o'clock.[4]

Radiograph examination of the vertebral column disclosed narrowing and calcification of the intervertebral regions of the dorsal and lumbar vertebrae (Fig. 1). These foci of calcification did not project beyond the limits of the anterior ligaments. There were several small marginal exostoses noted in these vertebral bodies, but no evidence of ossification of the anterior ligaments or ankylosis of the facets.* Calcification of the interpubic ligaments was present.[5]

Radiographic examination of the knees disclosed a marked irregularity and sclerosis in the subchondral region of the left patella and of the contiguous femoral articular surface. Small osteophytes were seen on the periphery of the articular surfaces of the tibia and femur of both knees. Several free roundish bodies were noted in the posterior compartment of the left knee (Fig. 2). No free bodies were seen in the right knee joint. Radiographic examination of the shoulder areas revealed a subchondral erosion on the glenoid portion of the left scapula. No calcification of the labrum of the glenoid was noted.

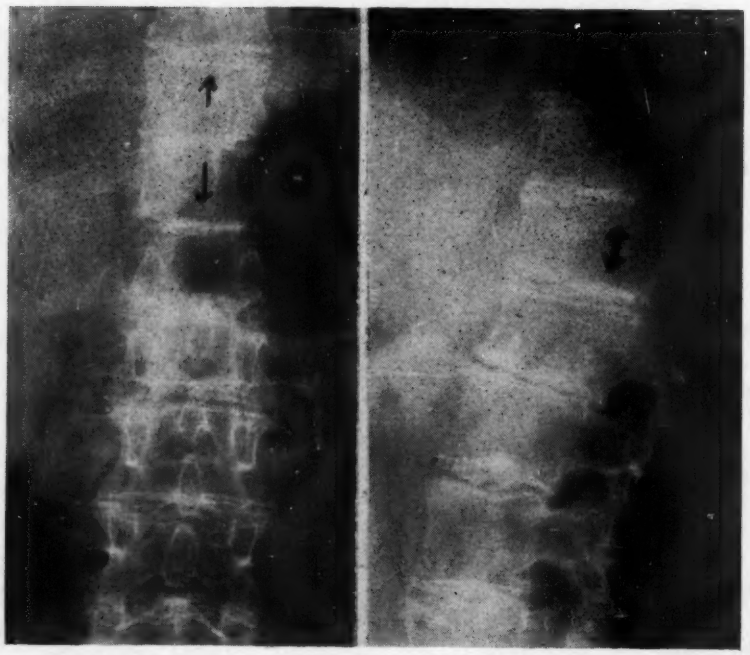
Study of the peripheral blood revealed a hemoglobin of 120 per cent (Sahli), a red cell count of 6 million per cubic millimeter and a white count of 7,250 per cubic millimeter. The differential count showed a normal percentage distribution of the white cells. The hematocrit reading was 51 per cent. The erythrocyte sedimentation rate was 0 mm. during the first hour.

Examination of the urine revealed that it was of yellow color, with a specific gravity of 1.012. The tests for albumin and sugar were negative. When the urine was left exposed

*Occasionally the radiographic picture of the vertebral column may simulate that noted in von Bechterew's disease.

to the air, it turned dusky brown. With the addition of a few drops of a solution of 5 per cent sodium hydroxide, the urine turned black on exposure to air. This reaction took place very readily when a current of air was passed through the alkalinized urine. Furthermore, the alkalinized urine produced an immediate black discoloration when it was applied to the surface of photographic contact print paper in daylight. This test is considered by Fishberg to be specific for alkaptonuria.[6] Alkaline extracts of the patient's hair, fingernails, saliva, stool, lacrimal secretions, and sweat failed to show this reaction on contact with photographic paper on exposure to daylight. Homogentisic acid was present in the urine and one study revealed the amount of 4.4 Gm. over a twenty-four hour period. The chemical

A.



B.

Fig. 1.—*A*, Lateral view of the dorsal vertebrae shows dense or opaque foci in the intervertebral regions. *B*, Anteroposterior and lateral views of the lower dorsal and of the lumbar vertebrae show similar changes.

examination of the peripheral blood disclosed normal amounts of sugar, nonprotein nitrogen, cholesterol, calcium, phosphorus, and alkaline phosphatase.

As surgical intervention was not indicated, no histologic studies could be made of the free bodies in the left knee. However, on the basis of the chemical findings in the urine and the radiographic examination of the skeleton, it was felt that the changes in the knee joint were part of the picture of alkaptonuric arthritis. The soldier was returned to civilian life.

Fig. 2.—Lateral view of the knee reveals several free bodies in the posterior compartment. Note the increase in density in the subchondral region of the patella and of the contiguous femoral articular surface.

DISCUSSION

It is believed that articular cartilage is prematurely degenerated when homogentisic acid is deposited in it. Such cartilage becomes highly friable, easily cracked, and is separated readily from the subcondral zone. These detached portions of articular cartilage may then either be deposited on the synovial lining or lie freely in the articular cavity. The articular cartilages and their free fragments may become pigmented and are prone to further degeneration and calcification because of a secondary disturbance in the metabolism or nutrition of the cartilages. These detached islands of cartilage form the nidus for the free bodies found in association with alkaptonuria and ochronosis. Furthermore, the semilunar cartilages of the knee may also become pigmented and calcified, particularly if they are scarred or fibrotic. The modified or frayed articular cartilages in general predispose to a premature secondary generalized osteoarthritis with all of its well-known complications. In a like manner the deposition of pigment and cartilaginous plaques on the synovial lining causes a proliferative villous synovitis. Of interest is the reported finding of osteoporosis in association with ochronosis.[7]

In considering some of the various other causes for abnormal coloration of tissues in association with arthritis, one must think of melanuria, chronic argyria, methemoglobinemia, hemochromatosis, porphyrinuria, carotinemia, Gaucher's disease, chloroma, neurofibromatosis, and fibrous dysplasia.

The predilection of the ocher pigment for the articular cartilages and the intervertebral tissues is of interest because a deposition of bile pigment, in

similar sites, was observed in experimental studies of mice. Histologic examination of musculoskeletal system of mice by means of fluorescent microscopy revealed that the ligation of the common bile duct caused a deposition of pigment in the articular cartilages, intervertebral disc, epiphyseal plates, and pulp of the teeth.[8] These experimental studies suggested that some of the pigment permeates into the articular cartilage from the surrounding synovial fluid and that there is a free exchange of tissue fluids in the intervertebral disc.

TREATMENT

Although the administration of vitamin C was suggested and has been tried for alkaptonuria and ochronosis, no definite improvement has been reported.[9] As for surgical treatment, this should be limited only to relieve "fixed locking" in the knee or any other large joint when caused by free bodies. In instances of severe osteoarthritis of the knee or hip, arthrodesing procedures are indicated.

CONCLUSION

The entity of alkaptonuria and ochronosis can be recognized by the presence of pigmentation of the nose, ears, sclera, and skin, by the detection of alkapton bodies in the urine, and by radiographic evidence of premature osteoarthritis of large joints and calcification of the intervertebral disc tissues. In the differential diagnosis of osteoarthritis, especially with the presence of free intra-articular bodies as noted on radiographic examination, consideration should be given to alkaptonuria as a possible etiologic basis. A case illustrating some of these findings has been presented.

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ARTERIOSCLEROTIC ISCHEMIC NECROSIS OF THE LOWER EXTREMITIES

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THE operative mortality in patients with arteriosclerotic occlusion of the vessels of the lower extremities is still unreasonably high. This is true in spite of the excellent contributions by many authors who are interested in this field of surgery.[1-8] The reported mortality has shown a reduction during the past decade from 30 to 40 per cent to 10 to 20 per cent. The improvement in surgery of peripheral arteriosclerosis has been largely accomplished by the following factors. In diabetic patients, close cooperation between the medical and surgical attendants has been shown by McKittrick[1, 2] to be of the utmost importance in the pre- and postoperative regulation of the patient's disordered metabolism. The recognition of an adequate arterial supply, in the presence of infection, may preserve many extremities by the adoption of conservative therapy. Penicillin and the sulfonamides are useful in the control of spreading infection, provided the blood supply is adequate. The correction of preoperative dehydration, acidosis, and hypoproteinemia has rendered many patients better operative risks. A guillotine amputation, performed as an emergency procedure, has undoubtedly reduced the mortality in the presence of spreading infection. The release of sympathetic vasomotor control, before ischemic necrosis has occurred, promises to save many arteriosclerotic extremities.[9-11] The arteriosclerotic patients who are candidates for sympathetic intervention must be selected carefully. It is well known that when the management of any disease is placed in the hands of one or two men who are interested in the details of diagnosis and therapy, the results improve. The mortality is still sufficiently high, however, to warrant intensive study of the various factors that contribute to the postoperative death of these patients.

It seemed to me that an unusually large number of preliminary or minor toe amputations had been performed at University Hospitals during the past twelve years. To determine the frequency with which thigh amputation was preceded by toe amputations, and the effect upon mortality, the following statistics were compiled.

Only patients with arteriosclerotic occlusion of the peripheral arteries were included. Although some of these patients had superimposed pyogenic infection, the main cause of disability was ischemia in every instance. Those patients who had amputations for severe infection in the presence of a clinically adequate arterial blood flow were excluded. The major amputations consisted of transection at either the mid-femoral or the supracondylar level. No Gritti Stokes, Callender, transtibial or transmetatarsal amputations were performed. The minor amputations consisted of removal of one or more toes and, in most

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TABLE I. GENERAL STATISTICS

Number of patients	104
Male, 64. Average age, 63.4 years	
Female, 40. Average age, 69.9 years	
Patients with minor amputations	27
Patients with major amputations	47
Patients with minor amputations followed by major within 3 mo.	30
Number of amputations	164
Major, 58	
Minor, 46	
Major and minor combined, 60	
Average time interval between minor and major amputations (combined)	23.4 days
Mortality	
Minor, 2.9%	
Major, 15.4%	
Total mortality (based on number of patients)	18.3%

instances, the distal head of the corresponding metatarsal bone. The anesthetic agents, ether, cyclopropane, intravenous sodium pentothal, spinal block, and refrigeration, varied so much that no group was large enough to be analyzed statistically. The patients were divided into staff and private as well as diabetic and nondiabetic. I believe there is no fundamental difference in the arteriosclerotic lesions in diabetic and nondiabetic patients.[12] The altered metabolism in the diabetic patient, however, increases the operative risk and these patients should be analyzed separately.

TABLE II. ANALYSIS OF 104 PATIENTS WITH AMPUTATIONS FOR ARTERIOSCLEROSIS OBLITERANS

	DIABETIC		NONDIABETIC		
	STAFF	PRIVATE	STAFF	PRIVATE	TOTAL
Minor	15	8	2	2	27
Major	10	10	11	16	47
Minor and major	16	7	7	0	30
Total	41	25	20	18	104

In 104 patients (Table I), there were 164 amputations, of which eighty-eight were major and seventy-six minor. Sixty-six of the patients were diabetic and thirty-eight were not (Table II). Sixty-one of the patients were cared for by the resident staff and forty-three had private attending surgeons. Of the fifty-seven patients who underwent toe amputations, thirty, or 52.6 per cent, were followed within a three-month period by a thigh amputation. Twenty-three of these thirty patients were staff and seven private. Twenty-three were diabetic and seven nondiabetic. Nineteen of the 104 patients died, giving a patient mortality of 18.3 per cent and an operative mortality of 11.6 per cent.

TABLE III. ANALYSIS OF 164 MINOR AND MAJOR AMPUTATIONS

	DIABETIC				NONDIABETIC				TOTAL	
	STAFF		PRIVATE		STAFF		PRIVATE			
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Minor	28	17.1	14	8.5	2	1.3	2	1.3	46	28.2
Major	15	9.1	11	6.7	14	8.5	18	11	58	35.3
Minor and major	32	19.5	14	8.5	14	8.5	0	0	60	36.5
Total	75	45.7	39	23.7	30	18.3	20	12.3	164	

Of the 18.3 per cent patient mortality, 12.5 per cent consisted of diabetic patients and 5.8 per cent of nondiabetic. The mortality for staff patients was 12.5 per cent, compared to 5.8 per cent for private patients. The average hospital stay for minor amputations was 31.3 days, for major amputations 39.2 days, and for combined major and minor amputations 39.6 days (Table IV).

TABLE IV. ANALYSIS OF HOSPITAL STAY, PRE- AND POSTOPERATIVE DAYS

	DIABETIC				NONDIABETIC				AVERAGE	
	STAFF		PRIVATE		STAFF		PRIVATE			
	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Minor	7.9	19.4	5.4	15	8	44	17	8.5	9.6	21.7
Major	11.2	30.4	8.8	33	11.5	37.6	10.4	13.8	10.5	28.7
Minor and Major	9.4	43.7	8	32.3	4.5	21	0	0	7.3	32.3
Average	9.5	31.2	7.4	26.8	8	34.2	13.7	11.2		

COMMENT

The fact that 52.6 per cent of the patients who had toe amputations were subjected to a thigh amputation within three months seems at first glance to indicate poor surgical judgment. Table VI shows that the operative mortality

TABLE V. CAUSE OF DEATH IN NINETEEN PATIENTS

NUMBER OF DEATHS	CAUSE
Coronary thrombosis	2
Cerebral thrombosis	1
Cerebral thrombosis or hemorrhage	1
Mesenteric thrombosis	1
Uremia, (?) nephrosclerosis	1
Progressive ischemic necrosis of leg	1
Progressive ischemic necrosis of stump	1
Pneumonia	4
Bronchiectasis	1
Pulmonary infarction	1
Stump infection	1
Welch Bacillus infection	2
Acute pyelonephritis	1
Failure of recovery from anesthesia	1

TABLE VI. ANALYSIS OF GROUP OPERATIVE MORTALITY

	NUMBER OF OPERATIONS	DEATHS	PER CENT
Minor	76	3	3.9
Major alone	58	9	15.5
Major preceded by minor	30	7	23.3

for the group of patients having combined operations is decidedly higher than the mortality for the group having only a thigh amputation (23.3 per cent to 15.5 per cent). Sixteen of the thirty patients having combined operations were staff patients with diabetes, who were admitted to the hospital with acidosis and a marked state of dehydration. In many instances, there was superimposed infection. In a few cases, permission for a primary thigh amputation was not granted by the patient or the family.

The successful toe amputations were performed only when necrosis was limited to the toe itself, when infection was minimal, and when there was some

evidence of at least a moderately satisfactory collateral circulation. If the results of toe amputations are to improve, the adequacy of the collateral circulation is probably the most important factor to estimate preoperatively. This is largely a matter of clinical judgment and can be best exercised by a surgeon experienced in evaluating peripheral blood flow. The location, type, and severity of ischemic pain, the rapidity with which pallor develops when the extremity is elevated, and venous filling time are useful in estimating collateral circulation. If the surgeon is not satisfied that healing will occur following removal of a toe, then a more radical type of primary amputation should be urged.

SUMMARY

Amputation of the lower extremities through the thigh when preceded by a minor amputation in patients with peripheral arteriosclerosis carries a higher mortality rate than primary thigh amputation alone.

The factors involved in deciding upon a major or minor amputation have been discussed.

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A SIMPLE PROCEDURE FOR THE CONTROLLED ADMINISTRATION OF INTRAVENOUS FLUIDS

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THE administration of intravenous fluids for the treatment of shock is undertaken usually with inadequate knowledge of the patient's circulating blood volume. During a recent study,[1] it became clear that simple methods for the determination of mean arterial pressure and of plasma volume would be desirable both as a guide to choice of therapy and as a means of assessing the therapeutic response. Hitherto, the equipment needed for this determination has been too cumbersome for use in the average hospital emergency or surgical ward. In the present study, a simple procedure was devised for the determination of plasma volume by means of a small visual comparator[2] and for the measurement of intra-arterial pressure by means of the Tycos aneroid manometer. Further, a kit has been designed to include in compact form all equipment needed for the administration of intravenous fluids, the measurement of mean arterial pressure, and the determination of plasma volume.

The salient features of the technique include the insertion of a small indwelling catheter into a medium-sized vein of the forearm and the insertion of a Lindeman type needle into the femoral or brachial artery. The indwelling venous catheter permits of dye injection for plasma volume determination and allows for repeated administration of intravenous fluids over a considerable period of time. The indwelling arterial needle establishes a convenient and reliable route by which blood samples for plasma volume determination and other laboratory tests may be obtained as well as providing a means of measuring mean arterial pressures.

DESCRIPTION OF THE KIT

The kit* illustrated in Fig. 1 consists of a wooden cabinet 18 inches long, 12 inches high, and 8 inches wide, the interior of which has been so designed as to permit ready access to almost every article. The list of contents and their disposition in the kit is given in Fig. 1.

Three of the instruments in the kit require further description. The first of these is the anestube syringe.† This is constructed of metal and is in fact no more than a metal frame with a piston. When loaded with the metal cap

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*Kit and contents supplied by Hellige, Inc., Long Island City, N. Y.

†Supplied by the Research Department of the Novocol Chemical Mfg. Co., Brooklyn, N. Y.

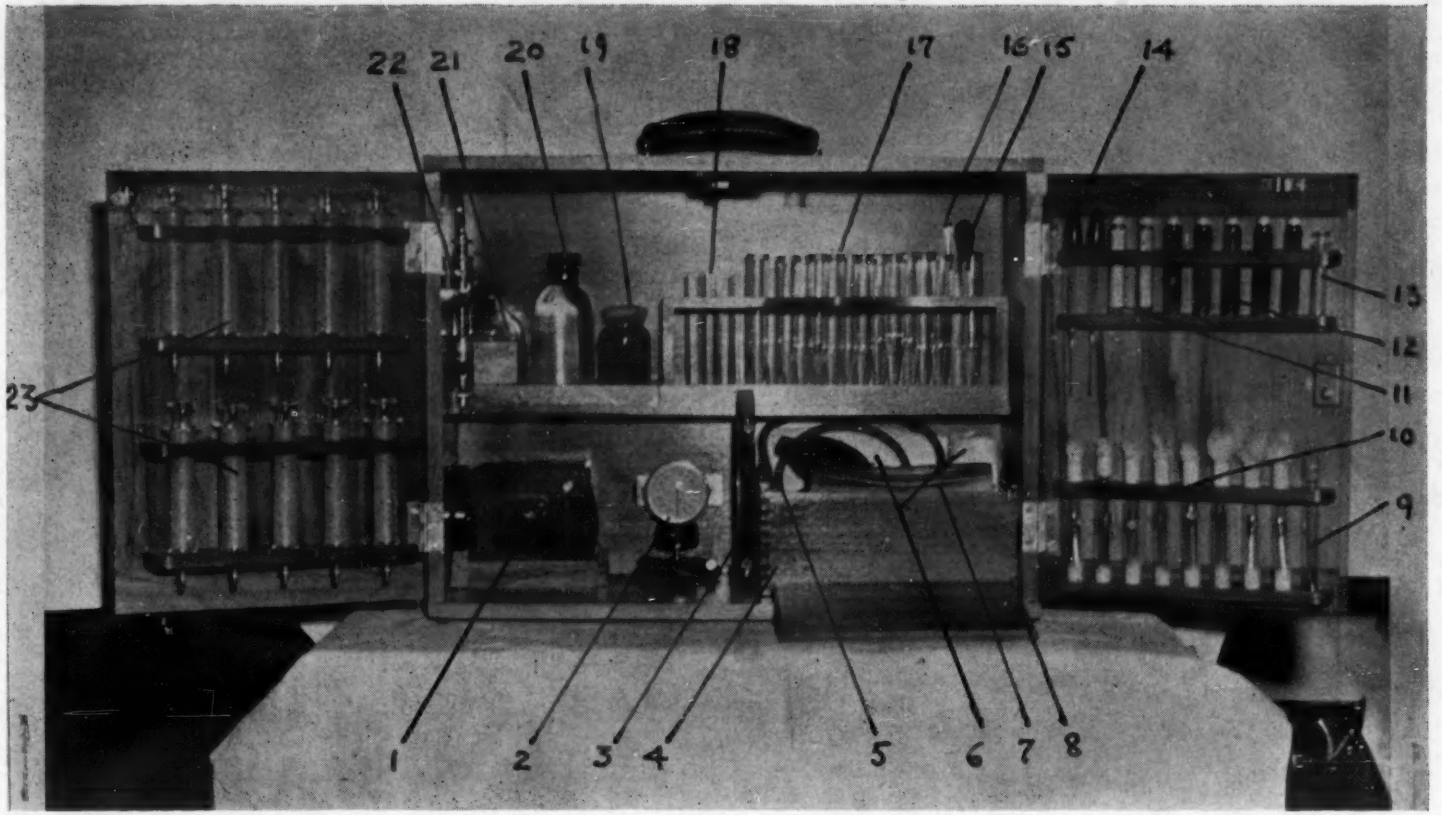

Fig. 1.—Kit for rapid blood volume determination and measurement of intra-arterial blood pressure. Key to symbols: *1*, Visual comparator; *2*, tycos aneroid with tubing; *3*, venous catheters; *4*, removable box; *5*, tourniquet; *6*, infusion set and Lindeman needles; *7*, blood pressure cuff; *8*, lid of removable box; *9*, syringe fittings; *10*, sterile needles; *11*, procaine anestubes; *12*, T-1824 anestubes; *13*, 2 c.c. syringe; *14*, pipettes; *15*, oil pipette; *16*, glass spatula; *17*, centrifuge and hematocrit tubes; *18*, square glass tubes; *19*, hydrogen peroxide; *20*, mineral oil; *21*, Na citrate solution; *22*, anestube syringe; *23*, 10 c.c. syringes.

"anestube," it is used like the ordinary syringe. The anestube syringe has been included in the kit because, together with the T-1824 anestubes,* it offers the most practical means of injecting an exact amount of T-1824 with minimal loss. Each anestube contains exactly 15 mg. of the blue dye T-1824 in 5 c.c. of normal saline solution. These tubes are made to deliver their contents within plus or minus 0.03 per cent but since aspiration is a feature of this syringe, the anestubes may be "washed" two or three times to insure delivery of all the dye. Such a system avoids using a specially calibrated glass syringe which must be filled from a separate ampule of dye—a less accurate and more time-consuming procedure.

The visual comparator† for plasma volume determination has been designed to measure the color of a single sample taken ten minutes after the intravenous injection of dye. The validity of this single measurement has been established by Noble and Gregersen.[3] Two color disks are supplied with the comparator: disk A is made up of ten colored glass standards which cover a range of total plasma volumes between 1,250 and 3,200 c.c. Disk B covers a range between 2,300 and 6,800 c.c. Each glass standard was made to match the color of a 10 mm. depth of a liquid standard of known dilution. The total plasma volume corresponding to each glass standard was calculated on the basis of a 15 mg. injection of T-1824. In the event, therefore, that more or less than 15 mg. of dye are injected, the true volume must be computed as follows:

$$\text{Disk reading} \times \frac{\text{mg. of dye injected}}{15} = \text{True volume.}$$

The reliability of this method for the determination of total plasma volume depends largely upon obtaining absolutely clear serum samples. This may be achieved readily if each blood sample is delivered into an oil-coated test tube. By this means, hemolysis is prevented. It is advisable, although not essential, to have each patient fast at least eight hours before study to avoid lipemia. If the sera are clear, color matching is not difficult. However, as in all colorimetric methods, individual judgment plays a major role. Some practice is necessary before discrimination between color differences in the high ranges is achieved. Results obtained with the comparator indicate that it measures plasma volume differences in excess of 5 per cent.

A simple method for the measurement of mean arterial pressure using the Tycos aneroid manometer has been devised. A 10 cm. length of rubber tubing, partially filled with citrate, is attached to the manometer. The free end, fitted with an adapter, is attached to the shank of the arterial needle. The mean pressure, recorded by the aneroid needle, is read directly from the face of the manometer. It requires less than a minute to make a single determination.

PREPARATION OF THE PATIENT

1. For the purpose of dye injection and the intravenous administration of fluids, a specially designed plastic venous catheter‡ is used. This is kept

*Supplied by the Research Department of the Novocol Chemical Mfg. Co., Brooklyn, N. Y.
†Supplied by Hellige, Inc., Long Island City, N. Y.
‡Supplied by the U. S. Catheter Company, Glenns Falls, N. Y.

patent either by means of a specially designed plastic stylet or by means of a slow saline drip. In the case of the latter, a saline infusion set is prepared in advance. The system is filled with saline solution, the catheter connected to a three-way stopcock at the end of the tubing, and the flow regulated to a slow drip. A medium-sized vein of the forearm is then exposed. The site of choice is distal to the junction of two or more tributaries so that, in case of difficulty, a portion of the vein proximal to the initial site will still be available for use. After local anesthesia, the vein is exposed under aseptic surgical technique making as small an incision as possible. Two silk ligatures are passed under the vein. The distal one is tied with a single knot to prevent back bleeding when the vein is opened. The proximal one is clamped and used as a sling to occlude the lumen above the point of incision when necessary. A transverse nick in the vein is made, the proximal lip of the opening caught in a fine clamp, the lumen thus held open while the tip of the catheter is introduced. The catheter should be passed into the vein for a distance of about 5 cm. and then tied in place with the proximal ligature. The incision should be protected with gauze pads and adhesive tape.

Although a No. 19 gauge needle may be used in place of a catheter and kept patent by the same means, the catheter offers certain advantages. Immobilization of the arm, once the catheter is in place, is not necessary. The arm may be turned and bent at will without displacing the catheter or interfering with the infusion. In addition, with as little as 6 drops of saline solution per minute, the catheter may be kept patent in situ for many hours thus permitting the administration of fluids at any time.

2. In order to measure mean arterial pressure and obtain blood samples readily, an indwelling Lindeman type needle is introduced into the femoral artery. In cases of shock, this artery is preferable to the brachial (or radial) where pulsations are often absent. The area *just* below Poupart's ligament, over the maximum arterial pulsation, as determined by palpation with the index finger, is first scrubbed with liquid soap, then cleaned with an antiseptic. Using the anestube syringe, with a No. 22 gauge needle attached and a cartridge of 2 per cent Procaine, the skin in this area is thoroughly infiltrated. The index finger is then placed over the infiltrated site and pressure applied over the artery so that it stays in a given position while the underlying tissues and, if possible, the coat of the artery itself are novocainized. With each forward thrust of the needle, care should be taken to pull back on the plunger to avoid injecting procaine directly into the arterial blood stream. It is advisable to infiltrate the tissues on either side of the artery as well as above and below the chosen route along which insertion of the arterial needle is to be made. When the area has been anesthetized, the arterial needle containing the patent stylet is grasped in the hand by the thumb, index, and second fingers, the thumb upon the flat end of the stylet, the index and second fingers upon the flange. While the index finger of the opposite hand applies sufficient pressure over the artery to fix its position but not to obliterate its pulsation, the arterial needle is driven slowly through the skin and underlying tissues at a point just below the index

finger at an angle of about 45 degrees. As progress is made in the direction of the pulsating vessel, the thumb is removed from the patent stylet at intervals to ascertain whether or not the artery has been punctured. When puncture of the artery has been accomplished, blood will be seen to drip from the patent end of the stylet. The flange of the needle is then grasped with one hand, the patent stylet with the other. Coincident with the slow removal of the patent stylet, the arterial needle is "threaded" into the lumen of the vessel. When the stylet has been removed, blood should spurt from the end of the needle. The solid stylet is then placed in the needle and stylet and needle together are threaded further into the vessel in order that a substantial portion of the needle shall lie within the lumen of the artery. It is advisable at this juncture to make sure that there is a free flow of blood from the needle by removing the stylet for a moment. As a precaution against clotting in the needle, the solid stylet should be dipped into the bottle of hydrogen peroxide before it is replaced. (During blood sampling, the stylet should stand in the peroxide.) As soon as the needle is in place, it should be taped securely to the thigh. Should the patient be under anesthesia or unable to lie quietly in bed, the leg should be immobilized by means of a restraint over the knee.

PLAN OF STUDY

The procedure recommended for the study and follow-up of a patient requiring controlled fluid therapy will be described under three headings: the pretherapeutic period, the period of therapy, and the post-therapeutic period.

Pretherapeutic Period.—During the first period, a single determination of plasma volume is made. This requires the withdrawal of a preinjection arterial sample, the intravenous injection of dye, and the withdrawal of a post-injection arterial sample exactly ten minutes later. In addition, measurements of pulse, respiratory rate, and mean arterial pressure are repeated two or three times. Should blood be required for hematocrit or serum protein determinations, this should be taken either before the injection of dye or after the withdrawal of the ten-minute arterial sample.

Period of Therapy.—Intravenous fluid is administered through the three-way stopcock and catheter. When the infusion or transfusion is completed, the saline drip is again started at the usual slow rate (6 drops per minute), or the plastic stylet is threaded into the venous catheter.

Post-Therapeutic Period.—All the measurements made during the pretherapeutic period are repeated shortly after transfusion or infusion and again a few hours later. The results will show the response of the patient to therapy and will serve as a guide to further management. Should there be gradual blood loss, as is sometimes encountered in a postoperative patient, this will be reflected in the measurements obtained. Although a fourth study can be undertaken six or seven hours after therapy, if necessary, it is not recommended because a fourth injection of blue dye may give a bluish tinge to the skin and mucous membranes. Although this is not harmful, it may be upsetting to the patient.

MEASUREMENT OF MEAN ARTERIAL PRESSURE

A 10 cm. length of gum rubber tubing with adapter secured at one end is held in the shape of a U by the left hand. A 5 c.c. syringe is filled with sodium citrate solution and used (without needle attached) to deliver approximately 2 c.c. of the solution into the free end of the tubing. This quantity will fill the tubing approximately to the halfway point. While the tubing is still held by the left hand in the U-shaped position, the aneroid manometer is fitted into the free end of the tubing with the right hand. Once attached, the tubing may be allowed to hang freely from the manometer without fear of losing citrate solution. The manometer and tubing are now ready for use, and should be placed upon the bed close to the arterial needle. With the left hand used to steady the arterial needle, the right hand removes the solid stylet. At the moment of removal, the thumb of the left hand is placed over the shank of the needle to stop the flow of blood while the stylet is placed in the beaker of peroxide. The adapter on the end of the aneroid tubing is then fitted into the shank of the arterial needle and the aneroid held in the upright position just above the level of the needle. If the oscillation of the aneroid needle is sluggish and the pressure mounts continuously, the system is not patent. The manometer and tubing should be detached, the tubing flushed with citrate and refilled. To insure patency of the needle, the stylet should be placed within the needle for a moment. The mean arterial pressure is taken as the average of the highest and lowest swing of the aneroid needle. This oscillation usually covers a range of from 2 to 4 mm.

DETERMINATION OF PLASMA VOLUME

Approximately 2 c.c. of heavy mineral oil are delivered into each of four centrifuge tubes. Next, the anestube syringe with Luer-Lok adapter attached is loaded with the dye cartridge, the cartridge locked in, and the piston screwed into the rubber plunger.

1. *Withdrawal of Dye-free Sample.*—A clean 10 c.c. syringe with adapter attached is used to collect the dye-free arterial sample. After withdrawal of the stylet, the syringe is fitted into the shank of the arterial needle and about 13 c.c. of blood are taken (more if hemoconcentration is present). Delivery of the blood into the oil-coated test tube requires a little practice. First the adapter is removed from the end of the syringe. The syringe is grasped in the right hand while the test tube is held in the left hand in a horizontal position and rotated slowly so that the entire inner surface of the tube becomes coated with oil. The horizontal position of the tube is maintained and the rotary motion continued while the tip of the syringe is placed against the inside surface of the test tube and about 5 c.c. of blood are delivered slowly. As the test tube is being filled, the tube and syringe are gradually brought into the upright position so that no spilling occurs. This tube is then replaced in the rack and a second tube coated with oil and filled in the same way from the same syringe. The purpose of the oil-coated test tube is to prevent hemolysis.

Experience has shown, however, that the oil-coated test tube is not indispensable; that if the blood is delivered slowly into a clean test tube without oil, a clear serum sample can often be obtained. It may be time saving, therefore, to take one sample without oil. A small amount of blood is held within the syringe for an hematocrit determination.* A few grains of purified heparin are placed in one of the Wintrobe tubes, a No. 19 gauge needle is attached to the syringe, and the remainder of the blood is delivered into the tube by placing the full length of the needle in the tube and giving a forceful thrust upon the plunger. In this way the tube may be filled to the top without trapping any air in its lumen. The tube is then placed in the rack and the blood stirred gently with a thin piece of wire. The time at which these samples are withdrawn is noted on the protocol sheet.

2. *Injection of Dye.*—The injection of dye should be undertaken with care so that none is lost. The tip of the anestube syringe (already loaded with the appropriate dye cartridge) is screwed snugly into the open arm of the three-way stopcock. The handle of the stopcock is then turned to permit direct injection of dye into vein and the dye injected. Accurate note is made of the time of this injection. Once the syringe has been emptied of dye, it is "washed" three times with saline solution from the infusion ampule. By manipulating the stopcock handle, saline solution is first aspirated into the syringe and then injected into the vein. In this way all of the dye is delivered into the circulation.

3. *Withdrawal of Ten-minute Sample.*—Ten minutes after the injection of the dye, another 13 c.c. of arterial blood are withdrawn from the femoral artery in the manner described, and the blood is divided between two sampling tubes and a Wintrobe hematocrit tube.

4. *Centrifugation.*—The duplicate dye-free serum and dye serum samples require ten minutes of centrifugation at approximately 2,000 r.p.m. This may be accomplished with a small angle centrifuge or, if need be, a hand centrifuge. After centrifugation, a clear layer of serum will be found to lie between the packed red blood cells and the oil. Should there be a fibrin clot in the serum, a small glass spatula is used to push it gently downward. In this case, centrifugation usually has to be repeated.

5. *Transfer of Serum.*—With two clean capillary pipettes, the dye-free and the dye samples are transferred into each of two square test tubes as follows: before introduction of the pipette into the oil, most of the air is expelled from the pipette. As the tip of the pipette is advanced through the oil, a few air bubbles are expelled from the pipette in order to prevent the entrance of oil into it. The tip is then advanced into the serum and the serum aspirated. In removing the filled pipette, care should be taken not to aspirate the oil. This may be prevented by maintaining slight pressure on the rubber bulb. The end of the pipette is then wiped with a piece of gauze and the sample delivered into the square test tube.

*This may be determined by the copper sulfate method.[4]

6. *Reading in the Comparator.*—A minimum of 2 c.c. of serum is required in each square tube for accurate readings. The square tube containing the dye-free sample is always placed to the left in the comparator, the dye sample to the right. Before placing the samples in the comparator, the appropriate disk should be selected and put in place. The comparator is then held close to the dye and the disk rotated until the color field on the left most nearly matches that on the right. When the best match is obtained, the plasma volume is read from the upper, right-hand corner of the apparatus where values corresponding to this color reading are registered in hundreds of cubic centimeters. When a sample cannot be matched to a given color disk, the nearest higher and the nearest lower reading should be taken and the value obtained by interpolation.

COMMENTS

This report describes a method for making repeated determinations of mean arterial pressure and of plasma volume in patients requiring controlled intravenous fluid replacement. A patient may be prepared for study and base line measurements obtained in less than twenty minutes. Utilizing this technique, thirty-eight patients with oligemia and hypotension have been studied. The results will be presented in a separate communication.[1]

In our experience, the method has been found most helpful as an aid to diagnosis and as a guide to therapy. The pretherapeutic measurements give information regarding the degree of hypotension and oligemia, and are therefore of assistance in determining the choice of intravenous therapy. Subsequent post-therapeutic values reflect the patient's response to therapy and indicate the need for further treatment.

The kit containing the equipment proved to be a useful adjunct. Because it could be easily carried from place to place, it made studies at the bedside or in the emergency ward practicable.

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ABSORBABLE FIBRIN TUBES FOR VEIN ANASTOMOSES

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IT WAS not until the advent of aseptic surgery that substantial progress was made in the field of vascular anastomoses. The most successful methods of restoring continuity in blood vessels may be divided into two general groups: (1) by careful, direct suture, and (2) by the use of mechanical devices.

The fundamentals of the suture method, established by such workers as Jassinowsky,[11] Jensen,[12] and Carrel[5] entail the use of very small needles and fine silk. In spite of the greatest care, thrombosis is a common cause of failure to produce a satisfactory anastomosis. The operating time required to complete such meticulous anastomoses by direct suture, and the disappointing results which frequently follow them, led several experimenters to develop methods whereby mechanical devices could be used for uniting vessels more quickly and more successfully.

At the International Medical Congress of 1897, Nitze[14] demonstrated the use of a small ivory ring. This was threaded over one end of a divided vein, which was then turned back over the ring so that the intima was exposed, and was secured by a circumferential ligature. The vein-covered ring was then inserted into the other end of the vessel and all these structures were held in place by a mechanical device not clearly described.

A magnesium prosthesis, similar in principle to Nitze's ivory ring, was described by Payr[15] in 1904. In the same manner, one end of a severed vessel was threaded through the metallic ring, turned back over the ring, and anchored with a circumferential ligature. This was inserted into the other end of the divided vessel and a second ligature held both parts of the artery (or vein) securely on the ring. Thus, the magnesium ring acted as a supporting structure and allowed the two vessel segments to be approximated intima to intima. This method was not uniformly successful. Magnesium, in the process of absorption, becomes a highly basic salt and provokes violent tissue reaction,[13] which may account for some of the poor results obtained. Payr minimized the distortion which was brought about by the gas-filled cysts and the extensive fibrosis produced by the magnesium disintegration.

Blakemore, Lord, and Stefko[1-4] have devised a highly successful "non-suture method" of vessel anastomosis, using rigid tubes made of vitallium—a material which excites little tissue response. The concept of using a vitallium tube lined with a vein graft to bridge an arterial defect is a unique contribution to military and traumatic surgery. Another field of usefulness for the Blake-

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This work has been carried out under contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

This paper is No. 54 in the "Studies of Plasma Proteins" of the Harvard Medical School, on products developed by the Department of Physical Chemistry from blood collected by the American Red Cross.

more technique is concerned with the establishment of venous shunts in patients with portal hypertension. In adults, the use of a vitallium tube has provided a satisfactory method for making such anastomoses. In contrast, this method of inserting a nonabsorbable tube has certain limitations when used in children because the vein lumen (at the anastomosis) cannot possibly increase in size during the subsequent growth of the patient.

This indicated limitation of the Blakemore tubes in children has prompted us to search for a material which (1) would be rigid, (2) would cause little reaction in animal or human tissues, and (3) would be absorbed by the host in a matter of several weeks or months. Such a substance would permit manufacture of tubes for performance of nonsuture methods of vascular anastomoses. If an appropriate material could be found and employed for vascular anastomoses in children, the subsequent absorption of the rigid tube would allow the vein (or artery) to expand and grow as the individual becomes older.

We were particularly attracted to the possibilities of fibrin film (prepared from human plasma by the methods of Ferry, Morrison, and associates[6-9]) since this material has already been studied by Ingraham and his associates,[10] who were interested in using it as a dural substitute. They tested fibrin film and found that it gave a minimum of tissue reaction (in monkeys and human beings) and was completely absorbed in six to eight weeks.

The present investigation is concerned with observations made during and after vascular anastomoses, using plasticized, fibrin cuffs to aid in vein reconstructions with a nonsuture technique. The fibrin was prepared by the blood fractionation laboratory of the department of physical chemistry at Harvard Medical School.*

Fibrin film is made from fibrin, plasticized by water and pressed into a thin sheet. Strips of this material, 2 or 3 cm. wide, were rolled around a glass rod of the desired diameter until the wall of the tube was 0.5 or 1.0 mm. in thickness. The seamless tube thus produced was left on its glass rod and placed in a test tube for steam sterilization. After sterilization, the fibrin cuff was slipped off the rod (under sterile conditions) and was placed in a stoppered sterile tube. It could be kept in this state indefinitely until it was used.

About ten minutes before a fibrin tube is to be used it must be placed in normal saline solution. This changes the firm leathery consistency of the dried film to a more pliable texture, the surface of which may be indented. In spite of this pliable quality of the tubing a circumferential ligature may be tied around it with only a minimal diminution of its internal diameter. As the fibrin tube absorbs fluids from the tissue in which it is implanted, it swells slightly, causing the circumferential ligature to become tighter and less likely to slip.

EXPERIMENTAL OBSERVATIONS

Dogs were used in all the experiments. The abdominal vena cava or a jugular vein was employed for the various anastomoses (Figs. 1 to 6). Twenty-

*Under the direction of Dr. Edwin Cohn. For the actual formation of the seamless tubes of fibrin film we are indebted to Dr. John D. Ferry and Peter R. Morrison.

Fig. 1.

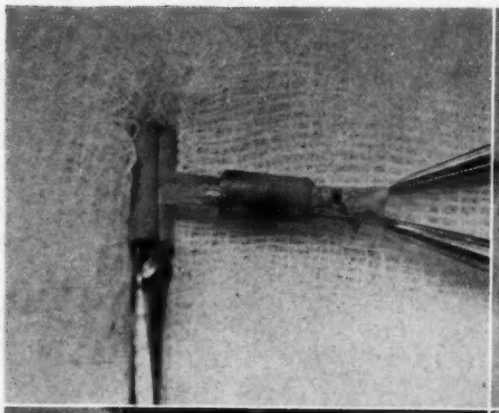
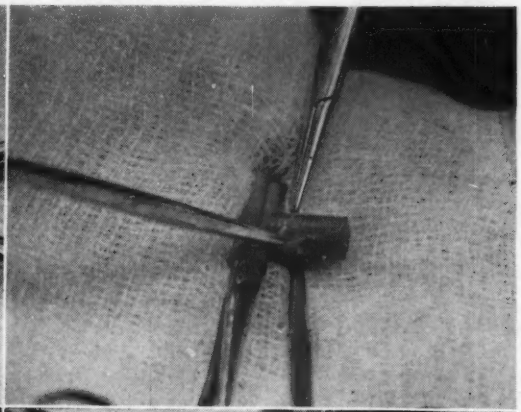


Fig. 2.



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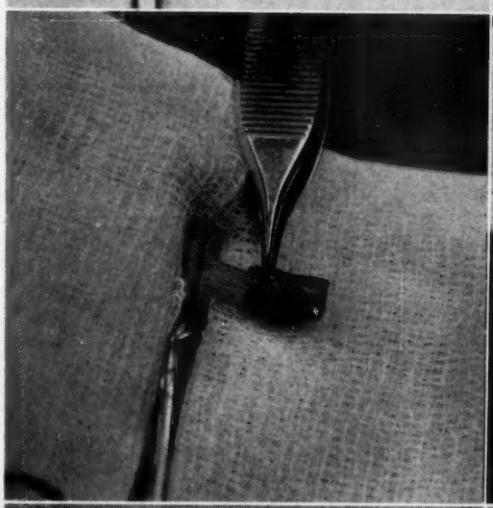

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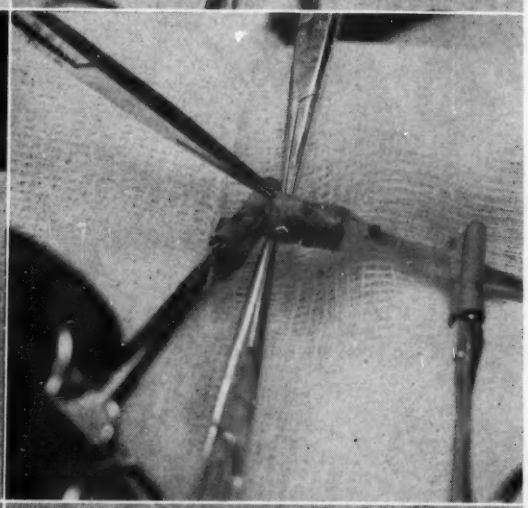

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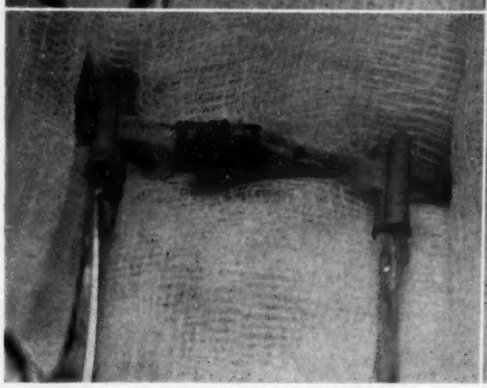

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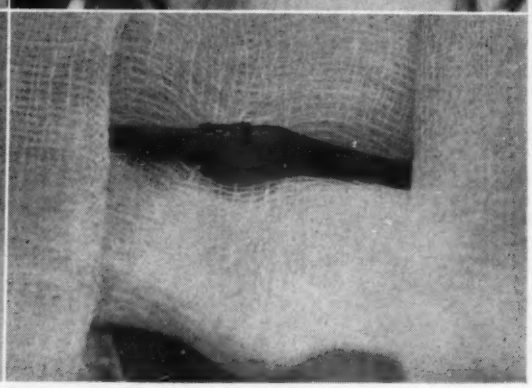

Fig. 1.—Beginning nonsuture anastomosis of vein. Fibrin film tube has been threaded on to proximal segment of vessel, which is compressed by rubber-covered clamp.

Fig. 2.—Vein has been turned back over fibrin tube by traction on three hemostats placed at equidistant points on cut end of the vein.

Fig. 3.—Turned-back vein held on fibrin tube by a fine chromic catgut circumferential ligature.

Fig. 4.—Distal segment of vein has been pulled on to the fibrin tube and the turned-back proximal vein.

Fig. 5.—Anastomosis completed by securing the distal end of vein over fibrin tube with second chromic catgut circumferential ligature.

Fig. 6.—Occluding clamps have been removed and blood is passing through the anastomosis.

seven anastomoses were carried out.* A rigid aseptic technique was used. Skin preparation consisted of mechanical scrubbing, using alternate sponges of zephiran and alcohol.

Fig. 7.—Vein exposed eight weeks after anastomosis. Lumen is patent. There is no thrombosis, or narrowing of lumen.

The jugular vein or vena cava was exposed for a distance of about 5 cm. and the vessel was occluded with rubber-covered clamps, gently applied. The vessel was then divided midway between the clamps and a fibrin cuff from 5 to 8 mm. in length was threaded onto the proximal segment. The end of the vein was then grasped with three fine-pointed hemostats and then turned back

TABLE I. SUMMARY OF DATA

ANIMAL NO.	VEIN EMPLOYED	ANIMAL SACRIFICED AFTER (NUMBER OF WEEKS)	FIBRIN CUFF REMAINING	RESULTS
W. S.	Jugular	4	None	Poor, no thrombus, 75% constriction of lumen
115-45	Jugular	8	None	Good, no thrombus, no constriction
120-45	Jugular	7	None	Good, no thrombus, some constriction
122-45	Right jugular	4	Yes	Fair, no thrombus
123-45	Left jugular	7	None	Good, no thrombus, no constriction
	Right jugular	7	None	Good, no thrombus, no constriction
125-45	Left jugular	3	Yes	Good, no thrombus
	Right jugular	3	Yes	Good, no thrombus
126-45	Left jugular	8	None	Good, no thrombus, no constriction
	Right jugular	8	None	Good, no thrombus, no constriction
127-45	Left jugular	18	None	Good, no thrombus, 20% constriction
	Right jugular	18	None	Good, no thrombus, 20% constriction
128-45	Left jugular	7	None	Good, no thrombus, slight constriction
	Right jugular	7	None	Good, no thrombus, slight constriction
129-45	Left jugular	6	None	Good, no thrombus, no constriction
	Right jugular	6	None	Good, no thrombus, no constriction
132-45	Vena cava	8	None	Good, no thrombus, 25% constriction
133-45	Vena cava	16	None	Good, no thrombus, 50% constriction
134-45	Vena cava	10	Yes	Good, no thrombus
135-45	Vena cava	5	Yes	Good, no thrombus
136-45	Vena cava	12	None	Good, no thrombus, 50% constriction
137-45	Vena cava	16	None	Lumen obliterated by regional fibrosis
138-45	Vena cava	2	Yes	Good, no thrombus
140-45	Left jugular	4	None	Good, no thrombus
	Right jugular	4	None	Good, no thrombus
141-45	Vena cava	3	Yes	Good, no thrombus
144-45	Right jugular	7	None	Good, no thrombus, slight constriction

*Following completion of the present work, similar anastomoses were made on arteries with satisfactory results.

over the fibrin cuff. A ligature of 0000 chromic catgut was tied over the turned back vein to hold it onto the cuff. Over this preparation the distal end of vein was then drawn (by three fine hemostats which grasped its end). A second circumferential ligature of 0000 chromic catgut was tied over this juncture, securely uniting the two portions of the vessel. The rubber-shod clamps were then removed. In no instance was there bleeding after the clamps were taken off. All wounds were closed with interrupted black silk sutures. The animals were kept for periods varying from two weeks to four and one-half months after operation.

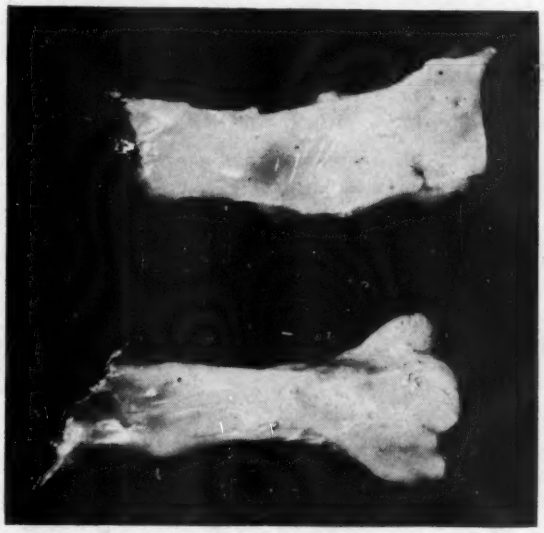

Fig. 8.—Two specimens of veins, removed eight weeks after nonsuture method of anastomosis employing an absorbable, fibrin tube. The intima is smooth and there is no intraluminal clot.

The selection of a fibrin tube of proper size is imperative for the success of an anastomosis. The cuff must be of such diameter that the vein can be easily turned back upon it, since stretching the structure over a tube of too great size will produce tears which invite thrombosis. Large dogs, weighing thirty to fifty pounds, were used for the jugular vein anastomoses. In these animals a fibrin tube 6 to 8 mm. in length, with an inside diameter of 4 to 5 mm., could be used.

RESULTS OF EXPERIMENTS

In Table I is given detailed information regarding the individual experiments. The condition of the anastomosed vein was studied in each case at a subsequent date by sacrifice of the dog, removing the vessel and making a careful gross and microscopic examination of the specimen. Thrombosis had not occurred in any instance. When opened, the vessel intima was smooth and glistening (Fig. 8) and the precise line of anastomosis was often difficult to identify. In twenty-six specimens the vessel had a lumen of satisfactory size. In several specimens there was a slight constriction of the vessel at the anas-

TABLE II. TIME OF DISINTEGRATION AND ABSORPTION OF FIBRIN CUFFS AS FOUND IN AUTOPSY EXAMINATIONS

	2 WK.	3 WK.	4 WK.	5 WK.	6 WK.	7 WK.	8 WK.	10 WK.	12 WK.	16-18 WK.
Dogs with fibrin cuff remaining	1	3	1	1				1		
Dogs with fibrin cuff disappearance	—		3		2	6	4		1	4

tomotic site. In one vena cava experiment the vessel had become obliterated by fibrosis resulting from extensive regional infection.

The time necessary for the absorption of the fibrin cuff is of considerable interest. The data are summarized in Table II. In dogs sacrificed before six weeks, three had no fibrin remaining and six had some of the cuff still in place. In animals kept more than six weeks only one had some film remaining. In short, the fibrin cuffs usually disappeared in six or seven weeks (Fig. 9).

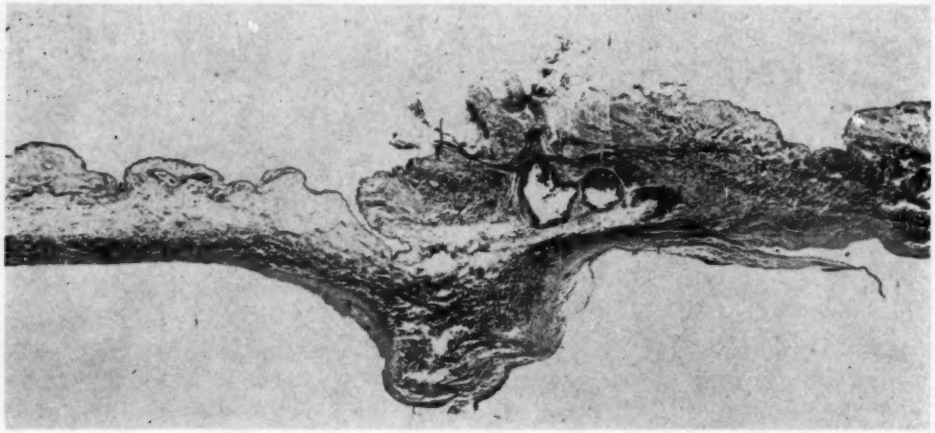

Fig. 9.—Photomicrograph of vein anastomosis, eight weeks after operation. The fibrin tube has disappeared.

CONCLUSIONS

Description is made of a nonsuture method of vascular anastomosis wherein the vessel segments are brought together over a fibrin cuff, making an intimal-lined reconstruction. The fibrin tubes disappear, usually in six or seven weeks. This leaves an anastomosis which is adequate in size, which is not constricted by a metallic ring (as in the Blakemore method), and which can enlarge in diameter with any subsequent growth of the individual.

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A SELF-RETAINING RETRACTOR FOR HEMILAMINECTOMY

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IN THE past few years several retractors have been designed for the purpose of giving adequate exposure in operations upon the spinal canal, and for the purpose of unilateral approach. In my experience they have failed to meet one or more of the following desirable features: adequate exposure, minimum interference in the operative field, absence of tendency to rotate when the blades are

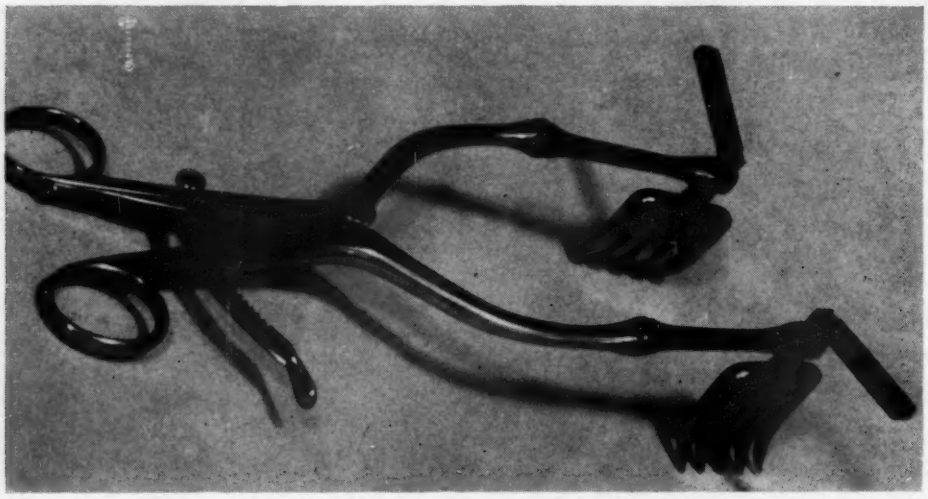

Fig. 1.—Showing the upright arms of the blades hinged so that they may be folded over and out of the operative field.

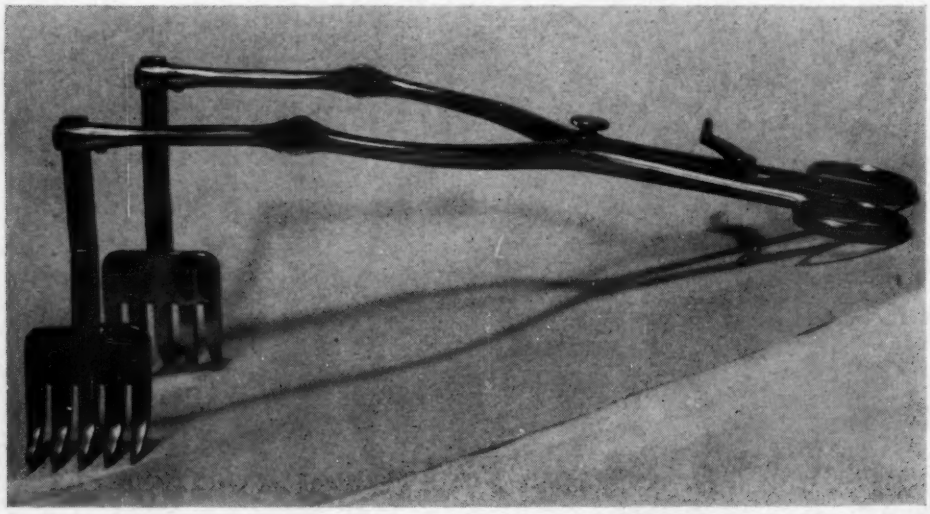

Fig. 2.—Showing that the blades of the retractor are adjustable to any required depth.

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set at different levels, and sufficient fixation of the blades in the soft tissues to keep the instrument from jumping out of the wound when force is applied. The retractor presented was designed with these requirements in mind and, in my experience, it has successfully fulfilled these requirements.

This retractor is a modification of other cerebellar self-retaining retractors. The upright arms of the blades are so hinged that they may be folded over and out of the operative field (Fig. 1), thus giving adequate exposure without interfering with the operator's approach. The tendency of a retractor to jump out of the wound when adequate retraction of the muscles is obtained has been overcome by the sufficiently sharp curve of the blades of this instrument. Adequate fixation of the opposing blade against the spinous process is also provided. In addition to its function as a hemilaminectomy retractor, this instrument gives satisfactory bilateral exposure in any region of the spine desired. The blades of this retractor are adjustable to any required depth, and are always at a right angle to the operative field (Fig. 2).

The blades of the retractor are 4 cm. in length, 3.8 cm. in width, and 0.5 cm. in thickness at the thickest part. The upright extensions of the blades are 6 cm. long and are hinged at 2.4 cm. from the shoulder of the blade itself. The angle of the blades varies from 0 to 52 degrees. The limbs of the retractor are also hinged at a distance of 6.5 cm. from the center of the slots which hold the upright extensions of the blades. The instrument was made by V. Mueller Co. of Chicago, according to my design.

VASCULAR SYSTEM OF THE LONG BONES OF THE RAT

SAMUEL M. REICHEL, M.D.,* ROCHESTER, MINN.

IN RECENT years there has been a considerable increase of interest in the supply and circulation of blood in the bones.[1-8] Various methods have been employed to overcome the many difficulties encountered in studying the circulation within such an intractable structure as bone. Among these have been the injection of radiopaque substances,[9] suspensions of fine carbon particles,[3, 8, 10] vital stains,[3] the study of serial sections,[3] and procedures in which part of the circulation to the bone is interrupted in the living animal.[6]

The present study is based on an adaptation to bone of the neoprene injection-corrosion technique which has been employed so successfully in vascular research on soft tissue. The injection material was a neoprene suspension supplied by the manufacturer in several colors, black and white having been employed in this work for best contrast. As received, the suspension was too thick for injection of capillaries and small arterioles, and therefore 40 parts of distilled water were added to 60 parts of neoprene suspension in the routine procedures. This material, when injected into blood vessels, coagulates spontaneously or when exposed to acids, alcohol, formalin, and many other substances, producing an elastic cast which conforms closely to the contours of the vessels. Such specimens have been preserved in alcohol (90 per cent) and in water for as long as two and one-half years and at the end of that time the neoprene casts were still elastic and strong.

Albino rats of both sexes and of weights ranging from 150 to 400 Gm. were employed in this work. In the rat the epiphyses are retained throughout life and do not fuse to the metaphyses at maturity as is the case in man. The bones studied were the tibia and femur. The animals were killed by bleeding under pentobarbital sodium anesthesia. The injections were made immediately into the abdominal aorta and the inferior vena cava. Prior to injection of the neoprene suspension, isotonic saline solution was perfused through the aorta until the perfusate returned grossly clear. The cannulae used were made of glass and their tips were carefully ground and beveled. The perfusate and neoprene suspension were warmed before injection to approximately 90° F. Mercury manometers revealed the injection pressures at all times during the injection. Arterial injections were made at 200 to 500 mm. of mercury, venous injections at 20 to 100 mm. of mercury. By means of a rubber bulb in the system, pulsations could be imparted to the injection fluid by the operator.

Following injection the two specimens were skinned and removed from the animal and placed in 90 per cent alcohol or in 10 per cent solution of formalin until studied. In a number of the specimens the vessels were dissected

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down through the soft tissues and traced to the bone. In others the bones were denuded and embedded horizontally in paraffin for one-half of their circumference. Then the exposed portion of the bone was corroded with concentrated hydrochloric acid or 25 per cent solution of sodium hydroxide or potassium hydroxide. Thus the injected vessels could be examined and studied in relation to the remaining bone. When the vascular relations had been studied, denuded bones were dropped into concentrated hydrochloric acid and the neoprene casts which remained, after corrosion was complete, were studied. Most of the specimens were studied in this manner (Fig. 1). Other specimens were placed in methyl salicylate, which is capable of clearing cortical bone and cartilage of

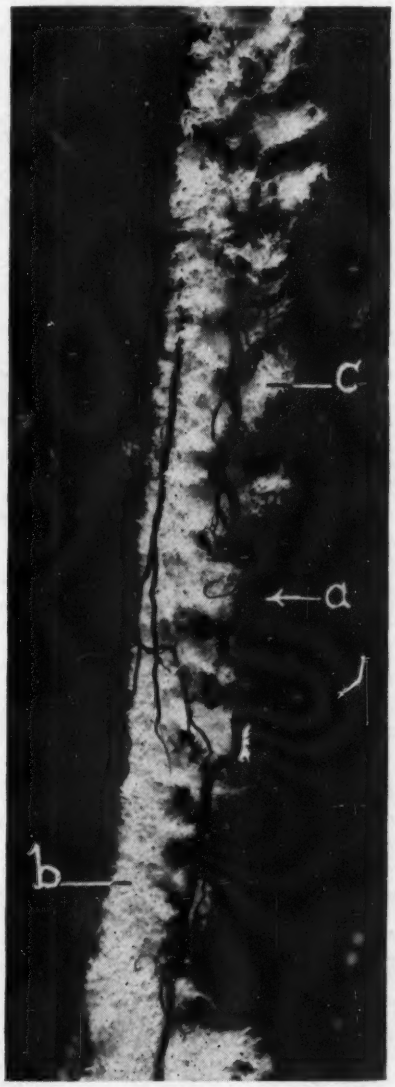

Fig. 1.—Portion of arterial and venous systems of bone marrow of femur showing vascular relations. *a*, Black neoprene casts are of branches of main nutrient arterial system. *b*, Venous central sinus is obscured by overlying freely anastomosing venous capillary sinuses although only a small percentage of venous capillary sinuses have been injected in this specimen. *c*, Communicating sinus (×9).

rats to a fair depth so that vessels could be visibly traced into the bone with ease and with certainty. Other specimens were imbedded in lucite, although this method of treatment had no advantages over other methods. Some specimens were decalcified and the vessels were dissected as they passed through the softened bone. In other specimens the cortical bone was removed locally by drilling, under water, with fine dental burrs.

GENERAL CONSIDERATION

Ordinarily, the higher the injection pressure the more complete was the injection of the specimen. With fairly high injection pressures, however, some of the vessels within the bone marrow ruptured and formed artefacts of two types. Where a vessel ruptured in the region of the endosteum there would be a dissection of the marrow from the bone by the extravasated injection fluid. a thin sheetlike artefact being produced. Where small arteries or arterioles were ruptured within the marrow substance proper, a rounded, cotton ball-like artefact was produced, with the artery approximately in the center of the mass. By treating these artefacts with xylol the rubber was softened and could be dissected down to the actual break in the vascular continuity. Artefacts were less common when the arteries and veins were injected simultaneously than when a single system was injected. When present, the artefacts were found most often in the metaphyseal regions.

Because of the long narrow shape of the tibia and femur the study of the neoprene casts of the marrow vessels was rather difficult. Examination had to be performed under water to minimize tangling of the elongated delicate branches of the nutrient artery. Even under the best conditions arterial capillaries often became entangled so that one could not be sure whether one was observing an anastomosis or an artefact. For this reason no statement can be made in regard to the occurrence of capillary arterial anastomoses.

Although the neoprene corrosion method was found to be an excellent means of studying the bones of rats, it is not believed that the efficiency of the circulation within a given bone can be gauged accurately by a study of the neoprene vascular casts produced by injection. There are too many variables involved and only a very rough approximation could be reached.

Regarding the importance of the nutrient vessels the literature contains a number of studies.[4-6, 11] The present study has indicated that, while the nutrient vascular system was well developed and profuse, there were other less conspicuous circulatory channels which were probably just as important as the nutrient vessels. Such arteries were small and individually capable of contributing only a modest increment to the blood supply of the bone. However, they were numerous and collectively could be considered an important source of blood. In the bones studied they were found to be most abundant in the distal half of the femur and the proximal half of the tibia (Fig. 2). None were found in the distal half of the tibial shaft. In their course along the surface of the bones the vessels rested in grooves similar to that of the main nutrient artery. They almost always entered the cortex in the same

direction as the main nutrient artery (proximally in the femur, distally in the tibia). After piercing the outer layer of cortex the vessels took a direct course to the marrow cavity. These arteries were traced into the marrow. For reasons mentioned previously it cannot be said, at this time, whether or not the vessels anastomosed with terminal branches of the main nutrient artery. Because of their characteristics they may be considered minor nutrient arteries.

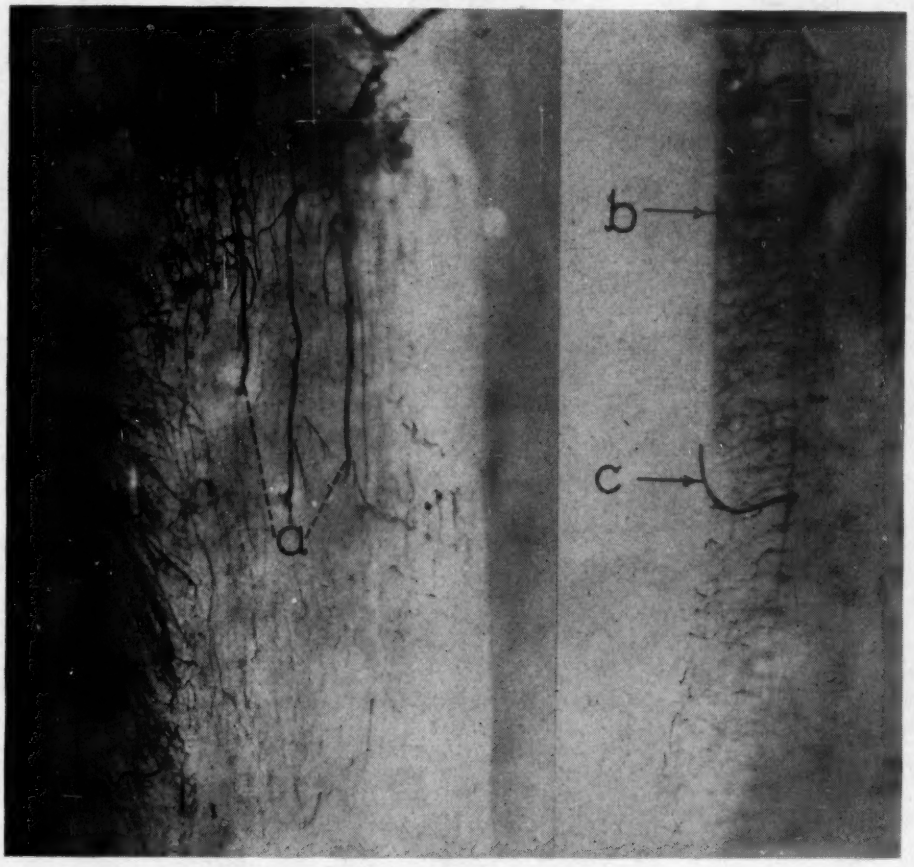

Fig. 2.—*a*, Minor nutrient arteries entering anteromedial aspect of proximal tibia. *b* and *c*, Minor nutrient arteries passing through cortex of femur. Longitudinal section of decalcified femur viewed on edge. In *b* bifurcation is demonstrated midway through cortex. (*a*, ×14; *b* and *c*, ×20).

The injection material used in this study demonstrated beautifully the profuse lacy network of periosteal vessels. These vessels could be traced easily into the Haversian system. The Haversian canals themselves received the injection medium only when high pressures were employed. Neoprene injection offers no particular advantage over other methods of study, in so far as Haversian vessels are concerned.

GROSS BLOOD SUPPLY OF FEMUR

The neoprene vascular casts revealed a surprisingly rich network of blood vessels in the femoral marrow cavity. The main nutrient artery entered the

marrow cavity by way of the nutrient foramen. The nutrient foramen was situated posteriorly in the upper third of the femoral shaft and perforated the cortex in a centripetal direction. Occasionally there were two nutrient arteries (with individual foramina) in close proximity. After reaching the marrow, the main nutrient artery gave off small proximal branches and then curved distally. Passing distally, the artery pursued a spiral path. Branches were given off, the larger of which also took a spiral course. It was not determined whether it was natural for such vessels to spiral, or whether this

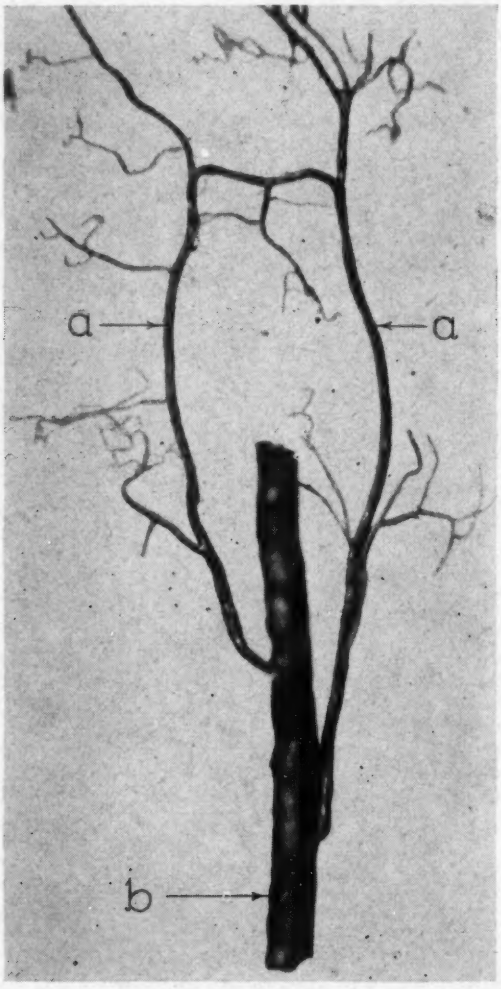

Fig. 3.—Anastomosis of arteries of bone marrow. Anastomosing vessels (*a*) are derived from the same parent vessel (*b*) (×65).

was an artefact due to high injection pressures. Because of the shape of the marrow cavity, arterial branches usually originated at a fairly acute angle. While most branches assumed the same direction as the parent vessel, an occasional small vessel traveled in the opposite direction. Anastomoses were occasionally found among the medium- and small-sized arterial branches (Fig. 3). The bulk of the arterial supply of the marrow was destined for the meta-

physeal regions, although some branches supplied capillaries to the central marrow and others to the peripheral marrow and the adjacent Haverian systems.

In addition to the main nutrient arterial system, the marrow cavity was also supplied by the minor nutrient arteries. These vessels were best demonstrated in the tibia and will be described later.

The nutrient vein, which accompanied the artery through the nutrient foramen, was a well-developed structure. Traced into the marrow cavity, it was seen to originate from the central sinus, a wide capacious channel extending the length of the marrow cavity and studded with innumerable branches of various sizes. Some of the branches, the communicating sinuses, were large and formed nearly a right angle with the central sinus. The communicating sinuses were most prominent when the central sinus was situated to one side of the marrow cavity. Occasionally the central sinus bifurcated as it approached the distal femoral metaphysis. The central sinus was in contact with the metaphyseal venous return by anastomosing venous channels. In addition to the nutrient vein, the venous system of the femur had two smaller veins leaving the distal metaphysis on its dorsal aspect.

The proximal epiphysis of the femur received arteries which entered circumferentially after passing along the subsynovial connective tissues lying on the neck of the femur. One vessel was found fairly constantly entering the anterolateral edge of the epiphysis. Two specimens were encountered in which definite arterial casts were seen crossing the epiphyseal line.

The distal femoral epiphysis received most of its arterial supply from the abundant circulation about the knee (Figs. 4 and 5). In addition, an artery entered the region of the intercondylar notch. The venous return was principally by means of a vein leaving the intercondylar notch.

GROSS BLOOD SUPPLY OF TIBIA

The main nutrient artery of the tibia was found in a groove on the posterior surface of the tibia. Proceeding distally, the artery perforated the cortex very gradually and at an acute angle. At about the junction of the middle and distal thirds of the tibia the artery reached the marrow cavity. Branches continuing distally were smaller than the main division of the artery, which curved and proceeded cephalad. The general distribution of branches and the spiral path were the same as in the femur. The pattern, however, differed, so that one could easily identify the bone injected by examining the arterial vascular casts thereof.

The minor nutrient arteries of the tibia were numerous in the proximal half of the tibial shaft. They entered the cortex in the manner described previously. Occasionally they bifurcated in the mid-region of the cortex (Fig. 2). Having reached the marrow cavity they proceeded in the most peripheral portion of the marrow. Rarely, a branch would be seen penetrating the marrow more deeply. Some arteries arborized freely but many coursed as single, fine, unbranching vessels for long distances. For the most part these arteries pro-

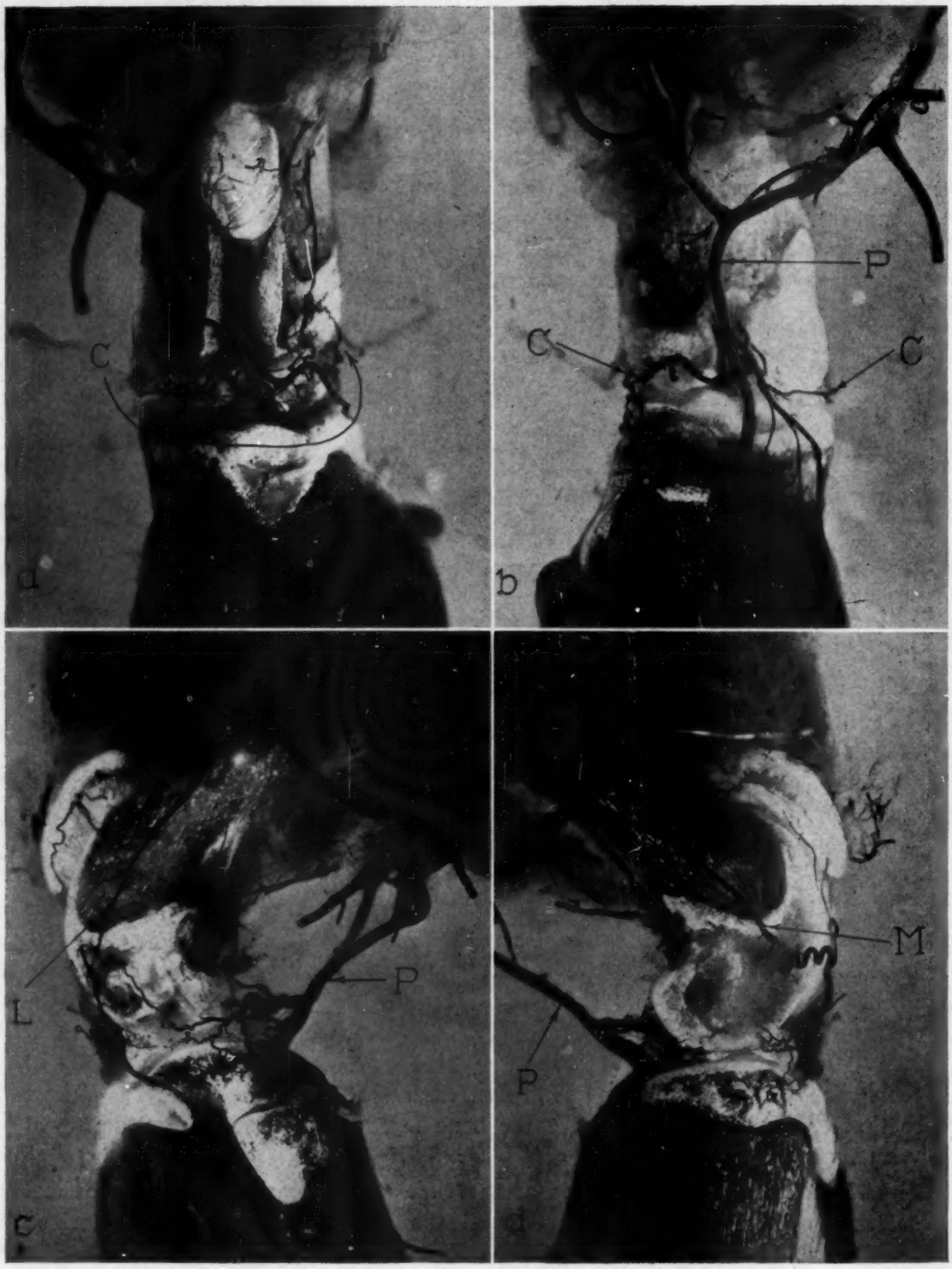

Fig. 4.—Four views of left knee, partially dissected and cleared in methyl salicylate. Arterial injection. Anterior view (*a*) and posterior view (*b*) show (*C*) circumferential anastomosis. *c*, Lateral view showing (*L*) lateral anastomotic circle. *d*, Medial view showing (*M*) medial anastomotic circle. *p*, Popliteal artery (×5½).

ceeded cephalad. They supplied the peripheral marrow and the adjacent Haversian systems with capillaries. These vessels were not found in the distal half of the tibial shaft.

Of considerable interest was the venous system of the tibia. An insignificant nutrient vein accompanied the artery through the nutrient foramen. The vein originated in the marrow cavity from a central sinus, which, in the distal half of the tibia, was seen to be of very small caliber and poorly developed. However, as it was traced cephalad the central sinus was seen to develop into a capacious structure with long communicating sinuses. The central sinus, having reached the proximal end of the marrow cavity, was seen

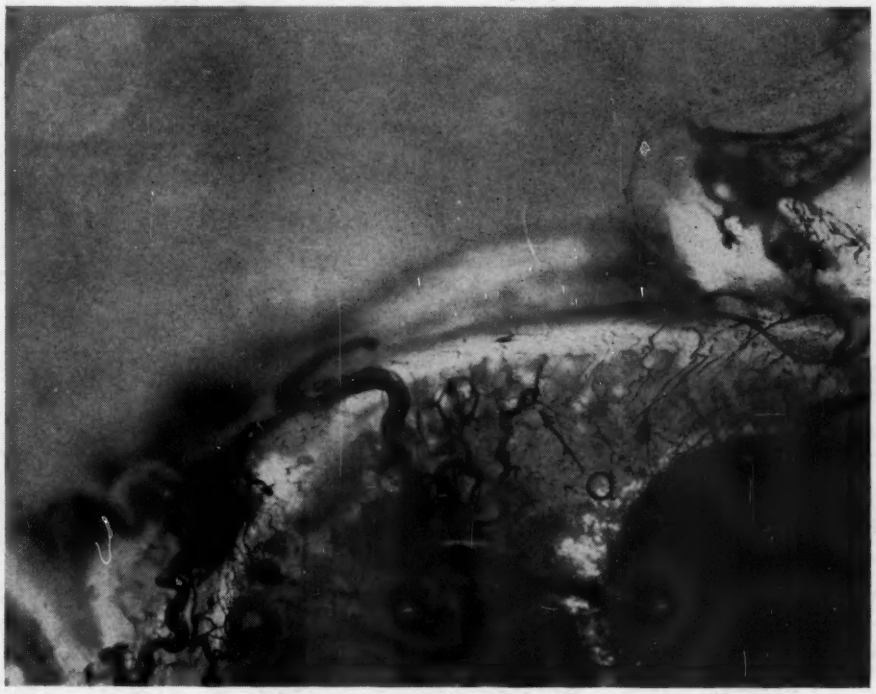

Fig. 5.—Side view of distal femoral epiphysis showing manner in which an artery (*a*) enters epiphysis (×14).

to leave the bone by way of a large vein which passed through a constantly occurring foramen on the posterior surface of the proximal end of the shaft (Fig. 6). There were also usually two additional small venous exits in the same locality.

The proximal tibial epiphysis was seen to receive an artery and vein regularly on its superior aspect just dorsal to the patellar tendon.

CAPILLARY STRUCTURE OF THE MARROW

It was unusual to obtain an almost complete filling of the venous capillary bed. When such a specimen was obtained the observer was impressed by the venous network. The cast remaining after corrosion had the shape of the marrow cavity. Obscuring all other structures was the interwoven network

of profuse, freely anastomosing capillary venous sinuses. These were so numerous as to make the cast feel and act exactly like soft sponge rubber. The arterial capillaries were very much finer than the venous sinuses. The venous capillary sinuses often had the shape of a cone with the arterial capillary uniting at the apex of the cone. In other instances the arterial capillary entered the flat side of a venous sinus (Fig. 7). Some venous sinuses were in close proximity to large arteries of the marrow and their casts were separated with difficulty.

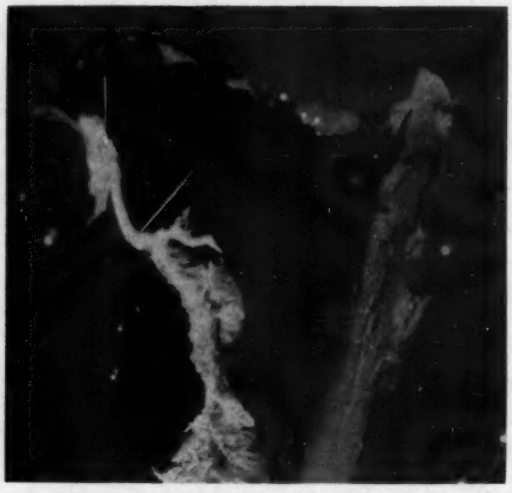

Fig. 6.

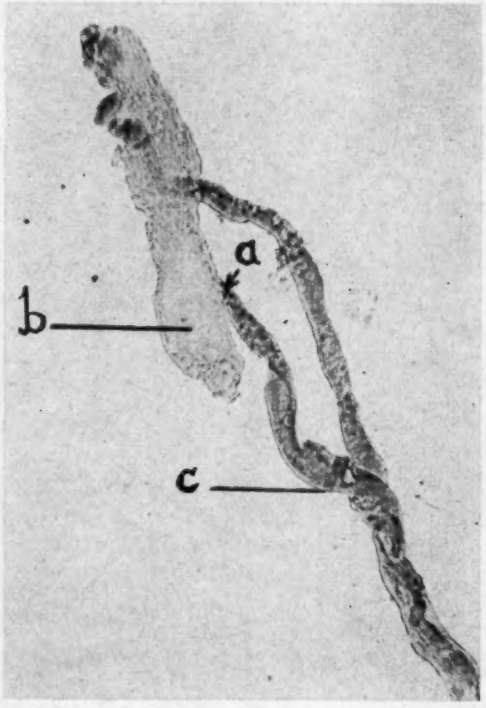

Fig. 7.

Fig. 6.—Proximal portion of tibia split longitudinally to reveal principal venous return from marrow cavity. Lines indicate location of foramen on posterior surface of proximal portion of tibia. Partial venous injection with white neoprene. Bone colored black for contrast (×20).

Fig. 7.—Cast of marrow capillaries. Specimen mounted under glass cover slip. *a*, Junction of arterial and venous capillaries. *b*, Venous sinus (white). *c*, Arterial capillary (black) (×365).

VASA VASORUM

The corrosion specimens showed excellent examples of casts of the vasa vasorum of the marrow arteries (Fig. 8). Although the vasa vasorum usually passed in the same direction as the parent artery, some took a reversed direction. Often several vasa vasorum were found in a short length of artery.

POSSIBLE DIVERSIONARY VALVES AT MOUTHS OF SMALL ARTERIES

V-shaped depressions in the neoprene casts just proximal to the mouths of arterioles were sometimes found (Figs. 8 and 9). Inasmuch as the neoprene casts are of high fidelity it can be assumed that the artery in this region either

Fig. 8.—Cast of (*a*) nutrient artery showing (*b*) vas vasorum. *c*, V-shaped depression just proximal to mouth of vas vasorum (×130).

dipped or was thickened. This finding was present only in some of the specimens, and then only where a small artery originated from a large artery directly.

Fig. 9.—Arterial cast illustrating V-shaped depression proximal to mouth of small branch (×85).

COMMENT

The anatomic arrangement of the vessels of the tibial marrow suggests significant implications. A liquid (blood) is pumped with pulsations into one end of the rigid tube (bone) which contains a thin-walled reservoir (central sinus and communicating sinuses). The reservoir drains at the opposite end of the rigid tube. Thus there is a mechanical arrangement which permits transfer not only of some of the arterial pressure, but perhaps even of pulsations, to the venous side of the vascular system. Such an auxiliary pump may be an important factor in the return of the blood from the lower extremities against the force of gravity while the body is in the standing position.

The minor nutrient arteries, besides supplying the cortex and marrow, may also be reserve structures which assume considerable importance when the

main nutrient artery is injured. Their presence might explain the results obtained in experiments in which the flow of blood was interrupted in the main nutrient artery. Their absence, as is the case in the distal tibial shaft, might explain the slow healing of fractures in this region.

With regard to the V-shaped depressions seen at the mouths of occasional small arterial branches, it is interesting to note that the apex of the V is always pointed upstream. This may signify the presence, in the wall of the parent artery, of a diversionary valve. Such a structure might prevent the full systolic thrust of blood in the large parent artery from reaching the mouth of the small branch.

The injection artefacts may also be of significance. They may indicate the course taken by extravasated fluid when a blood vessel of the marrow ruptures and may thus have clinical importance. Experimental work has shown that marrow infarcts become revascularized. However, where circulation is poor, as in the head of the femur, a vascular accident of this type might possibly leave a permanent cystic lesion. Acquired impairment of circulation, as in arteriosclerosis, plus a local vascular accident might also satisfy the requirements in an occasional case of idiopathic cystic bone lesion.

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In Memoriam

JOHN STAIGE DAVIS
1872-1946

IN THE death of John Staige Davis the Guild of Plastic Surgery has lost its mentor and its first dean.

Dr. Davis was born Jan. 15, 1872, in Norfolk, Va. He was the only child of the late Colonel Wm. Blackford Davis, M.C., U.S.A., and Kentie Howland Davis; he lived in frontier posts where his father was stationed until 1885, and then came east. He was a graduate of St. Paul's School in Garden City, Long Island, N. Y., and graduated from the Sheffield Scientific School at Yale University in 1895. He entered Johns Hopkins Medical School in the fall of 1895 and graduated in 1899, becoming a resident house officer in Johns Hopkins Hospital, serving under Dr. Osler, Dr. Halsted, and Dr. Kelly. Later he became resident Surgeon at the Union Memorial Infirmary under Dr. J. M. T. Finney where he remained for three years.

Dr. Davis was a keen observer, a seeker after facts, and a good clinician. For ten years he carried out research problems in the Hunterian Laboratory of Experimental Surgery and published a number of articles dealing with the results of his investigations. He was the author of *Plastic Surgery, Its Principles and Practice,* and throughout the years he published some seventy odd papers on plastic surgery in various medical journals. He was on the Editorial Board of SURGERY; was a founder member of the American Board of Surgery and of the American Board of Plastic Surgery; at one time was first vice-president of the American Surgical Association, president of the Southern Surgical Association, president of the American Association of Plastic Surgeons, and was a Fellow of a number of related bodies. He was also a founder member, and at his death a governor, of the American College of Surgeons.

When, in World War I, Surgeon General Gorgas appointed an officer of has staff to the duty of initiating a plan for early care and ultimate disposition of the face wounded, so prevalent in trench warfare, Captain Davis was one whose advice was first sought in the details of carrying out this assignment. When, after the war, it was realized that the same care was needed for a vast number of similar injuries in civil life, the Advisory Board for Medical Specialties of the American Medical Association was petitioned for authority to form an independent specialty board for Plastic Surgery. The authority was granted and Dr. Davis was chosen as the Board's chairman, a position he held until a short time before his death, and the successful establishment and operation of this Board was largely due to his sound judgment in difficult circumstances and his impeccable social and professional record. His Presidential Address for the Southern Surgical Association in 1940 is a classical

historic record of plastic surgery from the dim ages to our time, and in this article he established the fact that plastic surgery is next to the oldest of the surgical specialties.

Dr. Davis was associate professor of surgery (Plastic), Johns Hopkins University; visiting plastic surgeon, in charge of plastic surgery at Johns Hopkins Hospital; visiting plastic surgeon to the Union Memorial Hospital, Hospital for the Women of Maryland, and the Children's Hospital School. In June, 1946, he relinquished some of his more arduous duties and was named associate professor of surgery, Emeritus, at Johns Hopkins.

Dr. Davis is survived by his wife, Kathryn Bowdoin Davis, and their three children, Mrs. Charles E. Scarlett, Jr.; Dr. W. Bowdoin Davis, and Howland Staige Davis. Throughout his life his intelligence, his kindly disposition, and his good humor brought hosts of friends and admirers, and no task was too great for him if it was to help a friend. This at times was made difficult by overwork but was overcome by the sunshine of his kindly disposition. He passed on quietly Dec. 23, 1946, after a full day's work, leaving many, many regretful friends.

—Vilray P. Blair.

Book Reviews

The Differential Diagnosis of Jaundice. By Leon Schiff, M.D. Pp. 313. Chicago, 1946. The Year Book Publishers, Inc.

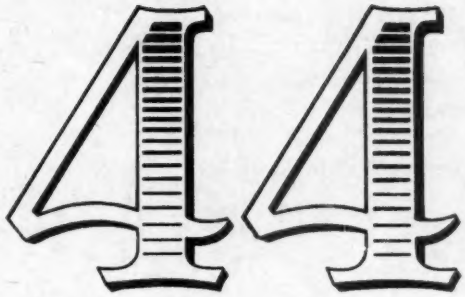
This is an excellent monograph. The author adheres closely to the objective as set forth in the title. Schiff, an experienced clinician, has presented in surprisingly few pages a very clear discussion of the clinical and pathologic disorders accompanied by icterus. The diagnostic features of case history, of physical findings, and of pertinent laboratory data are skillfully blended.

The literature of the last decade is very completely covered; each citation of a reference serves to emphasize a practical clinical feature without, however, interrupting the continuity of the paragraph. The monograph is clear, concise, and pleasant to read.

Many of the laboratory procedures so useful in the differential diagnosis of jaundice are quite recent. Anyone interested in them must refer to a number of articles scattered throughout scores of journals. This book describes the most useful of these so-called tests of liver function, not in the fashion of a laboratory manual but in a manner that is certain to prove appealing and instructive to the practicing clinician. Carefully weighing the merits and limitations of these laboratory aids, the author amply demonstrates the fashion in which they can be of great help when properly correlated with findings at the bedside. The inclusion of concise case histories brings out exceptionally well this type of clinical approach to diagnosis. The inclusion of an appendix containing specific laboratory directions for the tests that the author has found useful in clinical practice adds to the value of the book.

The chapters on calculous and cancerous jaundice contain a great deal of practical value to both surgeon and internist. The apparent frequency with which jaundice appears to develop following transfusions of plasma and whole blood or the administration of blood products makes it essential that surgeons familiarize themselves with this relatively new form of parenchymal liver disease, homologous serum jaundice. This subject is dealt with adequately in a special chapter.

The surgeon will find this concise volume exceedingly useful. It is highly recommended.



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